ST. LIDETA HELTH SCIENCE COLLEGE & BUSINESS

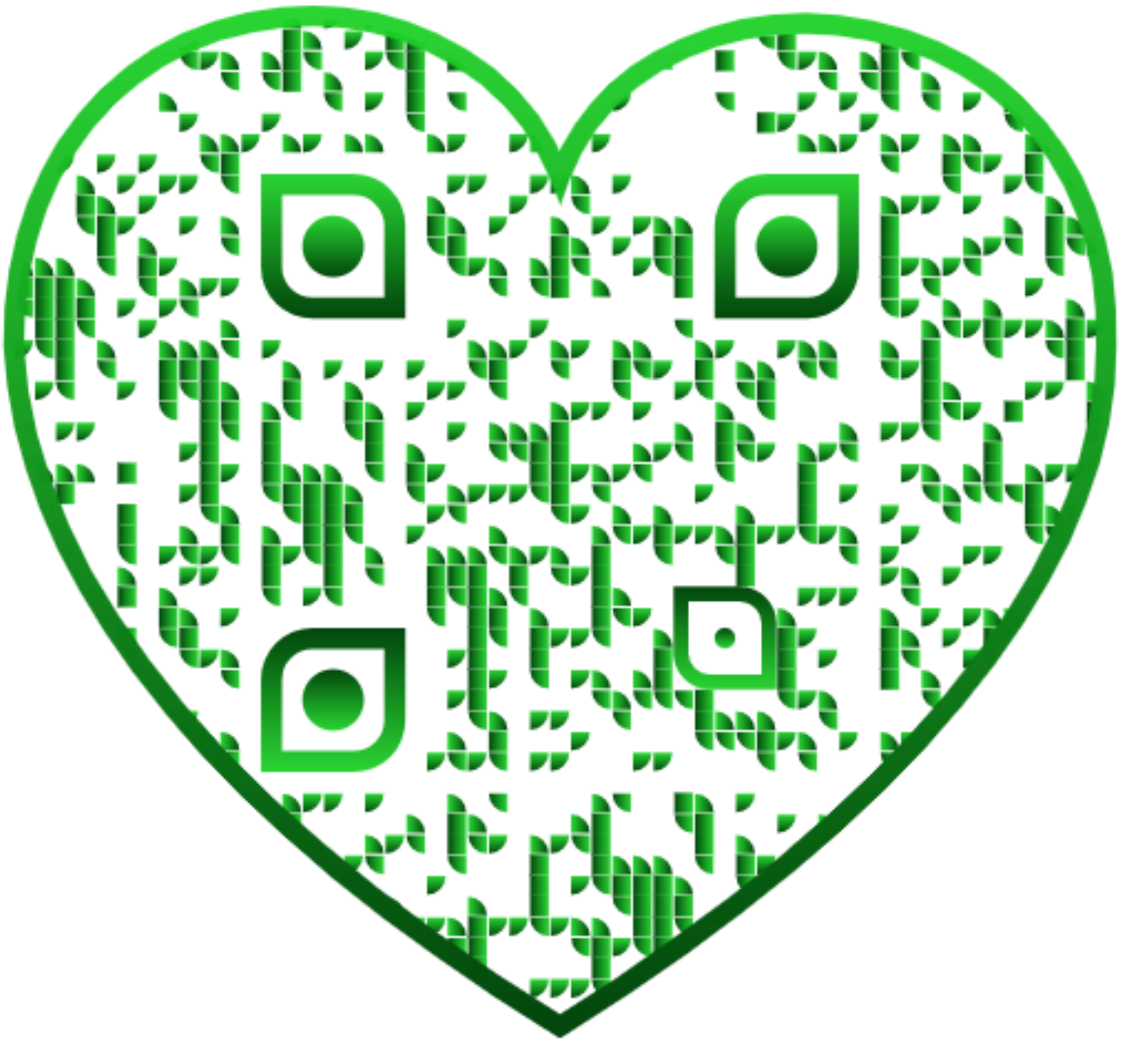
Course title: Biopharmaceutics & Clinical pharmacokinetics…4cr.hrs

Lecture note for Clinical Pharmacy degree students

Instructor: Tesfu Negussie

Qualification:

- MPH
- MSC
- BA
- Bpharm



Course Synopsis

1. Introduction to physiology of membrane
2. Factors influencing gastrointestinal drug absorption
3. Mechanisms of drug absorption
4. Principles of bioavailability of drugs
5. Bioavailability from non-oral routes of administration
6. Drug absorption
7. Drug distribution
8. Elimination of drug
    - 8.1. Drug metabolism: Phase-I & phase-II reactions, Pharmacogenetic
    - 8.2. Drug excretion: Renal and non-renal excretion
9. Pharmacokinetics Concepts & models
10. Non-linear pharmacokinetics
11. Pharmacokinetics in renal impairment
12. Pharmacokinetics in hepatic dysfunction
13. Pharmacokinetic drug interactions
14. Application of Pharmacokinetics to Clinical Situations
    - 14.1. Design of dosage regimen
    - 14.2. Individualization of drug dosage regimens
    - 14.3. Therapeutic drug monitoring
15. Immuno-suppressants

B. Teaching methodology

- Lecture
- Discussion

C. Assessment methods

- Assignment = 20%
- Mid-exam = 40% ……..[Covers Unit 1-5]
- Final exam = 40% ……[Covers the rest units]

Total = 100%

D. References

1.Gibaldi,M., Biopharmaceutics & clinical pharmacokinetics

2. Aulton M.E.,Pharmaceutics: The science of dosage form design, 2nd ed.

3.Shargel L. Applied Biopharmaceutics & pharmacokinetics, 2nd ed.

4.Lecture note prepared by Tesfu Negussie [Pharmacist]

Part I: Biopharmaceutics

1. Introduction
2. Factors influencing gastrointestinal drug absorption
3. Mechanisms of drug absorption
4. Principles of bioavailability of drugs
5. Bioavailability from non-oral routes of administration

Part I: Biopharmaceutics

Unit 1: Introduction

A. Definition

What is Biopharmaceutics ?

Bio = Life

Pharmaceutics: General area of study concerned with formulation, manufacture, stability & effectiveness [performance] of pharmaceutical dosage forms.

Biopharmaceutics: Study of the factors influencing bioavailability of drug and the use of this information to optimize pharmacological or therapeutic activity of drug products in clinical application

Or

The study of the relationship between dosage formulation & the therapeutic response

Biopharmaceutics

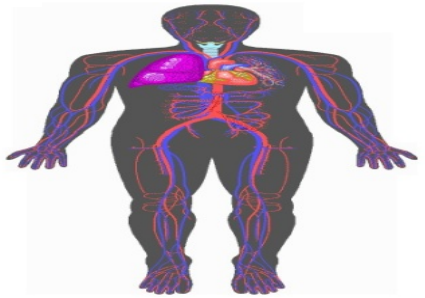
- The study of the interrelationship of physicochemical properties of drug & drug product based on biological performance of drug **or**
- Biopharmaceutics examines the interrelationship of physical/ chemical properties of drug, drug product and route of administration on rate & extent of systemic drug absorption.
- Biopharmaceutics uses quantitative methods & theoretical models to evaluate effect of drug substance, dosage form and routes of drug administration on therapeutic effect of drug & drug product in a physiological environment

- Studies in biopharmaceutics use both in-vitro and in-vivo methods.

  - **In vitro methods** are procedures employing test apparatus and equipment without involving laboratory animals or humans

  - **In vivo methods** are more complex study procedures carried out in human or animal or on cell or tissue taken from them.

Note: These methods assess impact of physical & chemical properties of drug, drug stability & large-scale production of drug and drug product on biologic performance of drug



Drug & Drug product performance

Drugs are substances intended for diagnosis, cure, mitigation, treatment, or prevention of disease. They are given in a variety of drug products hence, rarely used as pure drug substances

Drug products/finished dosage forms are drug delivery systems that release & deliver drugs to site of action to elicit desired therapeutic effect. They are formulation or matrix containing drug

Drug product performance is defined as release of drug substance from drug product at predetermined rate & extent for local or systemic drug action

Drug action refers to interaction of drug with receptor or enzyme systems to induce response due to alteration in biologic processes

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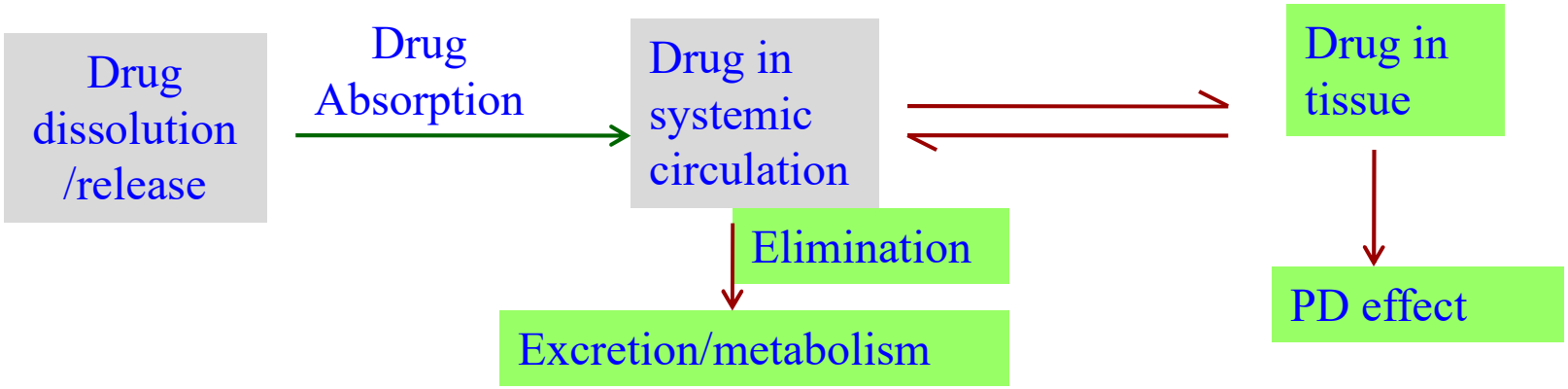
B. Aim of Biopharmaceutics:

- To adjust delivery of drug to the general circulation so as to provide optimal therapeutic activity for the patient

C. Scopes of biopharmaceutics

Biopharmaceutics deals with factors that influence:

- ❖ stability of drug within drug product
- ❖ release of drug from drug product
- ❖ rate of release of drug at absorption site
- ❖ systemic absorption of drug



NB:

Nature of drug molecule, route of delivery & drug product formulation can determine whether administered drug is therapeutically effective, toxic, or has no apparent effect at all.

Examples

- Intravenous isoproterenol causes increase in heart rate while same oral dose level has no observable effect on the heart
- Intravenous insulin decreases hyperglycemic state to normal while same oral dose level has no effect on hyperglycemia

Unit 2. Main factors affecting oral drug absorption (14hrs)

2.1. Physiological factors affecting oral absorption (6hrs)

2.1.1. Membrane physiology

2.1.2. Passage of drugs across membranes

Active transport, Facilitated diffusion, Passive diffusion, Pinocytosis, Pore transport, Ion pair formation

2.1.3. Gastrointestinal physiology

Characteristics of GIT physiology and drug absorption, Gastric emptying time and motility, Effect of food on drug absorption, Double peak phenomena, Malabsorption

2.2. Physical-Chemical Factors Affecting Oral drug absorption (6hrs)

pH-partition theory, Lipid solubility of drugs, Dissolution and pH, Salts, Crystal form, Drug stability and hydrolysis in GIT, Complexation, Adsorption

2.3. Formulation Factors Affecting Oral drug absorption (2hrs)

Solutions, Suspensions, Capsules, Tablets

2.1.1. Gastrointestinal membrane physiology

- Gastrointestinal membrane separates the lumen of the stomach and intestines from the systemic circulation
- It is the main cellular barrier to the absorption of drugs from the gastrointestinal tract
- It is complex in nature, being composed of proteins, lipids, lipoproteins and polysaccharides, and has a bilayer structure
- It is a semipermeable membrane, allowing rapid transit of amino acids, fatty acids, sugar & other nutrients & impermeable to plasma proteins

- The membrane can be viewed as a semipermeable lipoidal sieve, which allows the passage of :
  - ➢lipid-soluble molecules across it
  - ➢water and small hydrophilic molecules through its numerous aqueous pores.
- In addition, there are a number of transporter proteins or carrier molecules that exist in the membrane and which, with the help of energy, transport materials back and forth across it.

2.1.2 Mechanisms of drug transfer across membrane

1. Passive diffusion
2. Carrier- mediated transport
    A. Facilitated diffusion
    B. Active transport
3. Pore transport
4. Ionic or Electrochemical diffusion
5. Ion-pair transport
6. Endocytosis
7. P-glycoproteins

- There are two main mechanisms of drug transport across the gastrointestinal epithelium:

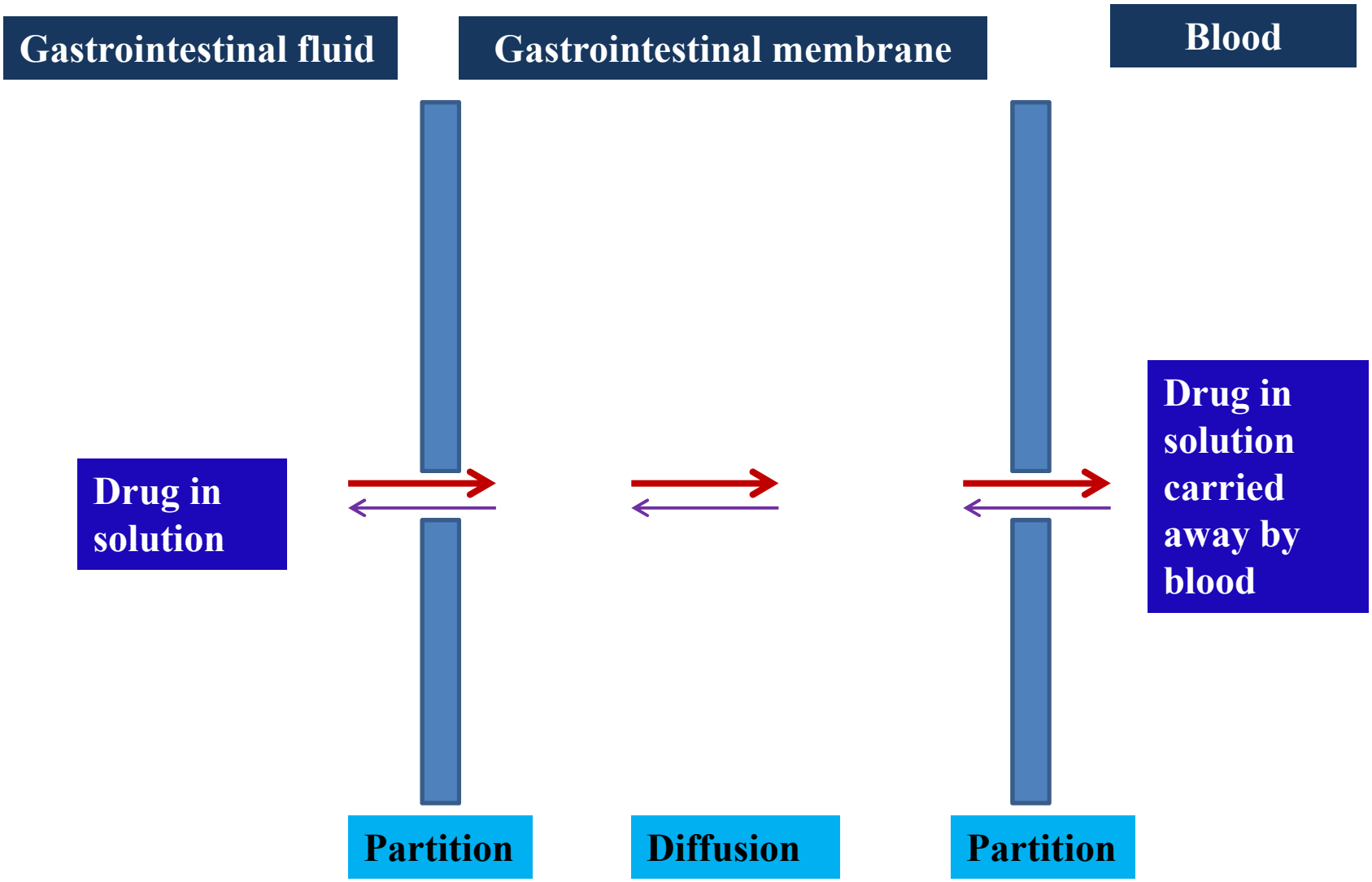
1. Transcellular: Across the cells
    - ❖ Simple passive diffusion
    - ❖ Carrier-mediated transport
        - ▪ Active transport
        - ▪ Facilitated diffusion
    - ❖ Endocytosis
2. Paracellular: Between the cells

Note:

Irrespective of types of drug transport mechanisms, drug molecules must be in solution to be absorbed (with the exception of drugs included in some last-generation pharmaceutical carriers, such as nanocarriers)

Passive diffusion [Non-ionic diffusion]

- Preferred rout of transport for small lipophilic molecule
- Rate of transport is determined by physicochemical properties of the drug, nature of the membrane & concentration gradient of the drug across membrane
- Involves partitioning of drug between gastrointestinal fluid / lipoidal membrane barrier interface followed by simple diffusion across the barrier. Then drug in barrier membrane partitioned between membrane epithelium & blood
- Involves absorption of 90% of drugs
- No competition b/n molecules
- No saturation of the process
- Blood carries away the drug creating sink condition

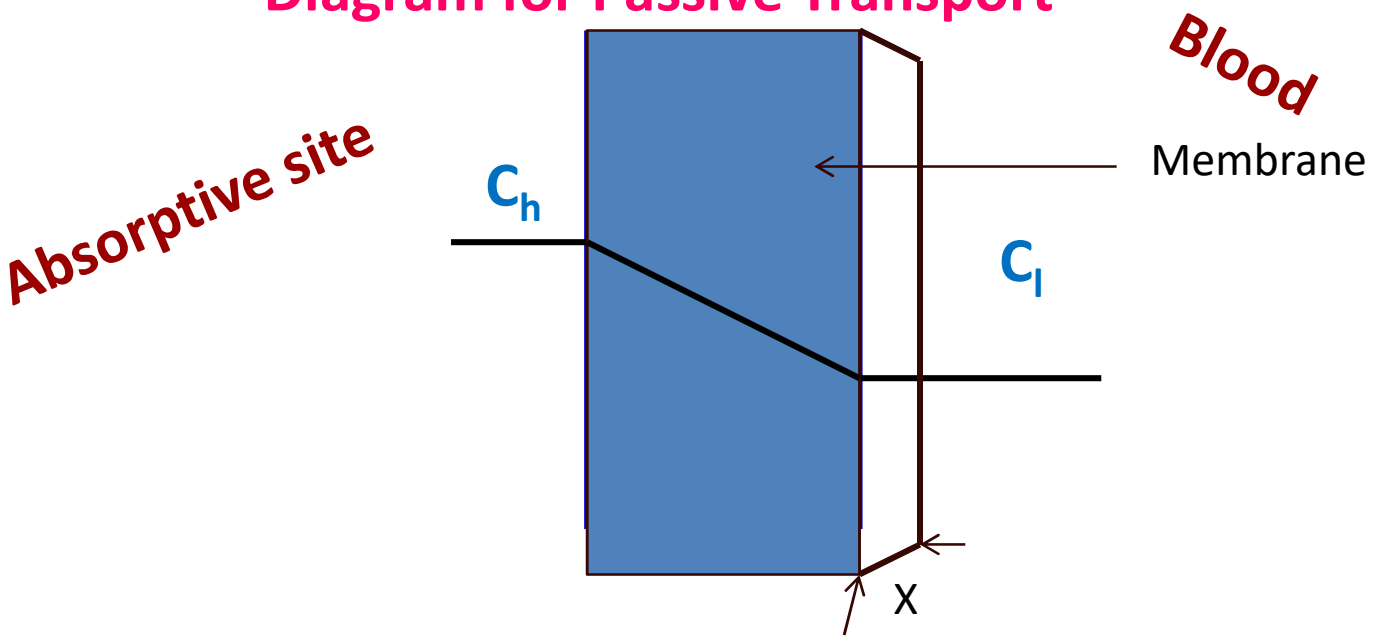


Drug absorption via passive diffusion

Passive diffusion is best expressed by Fick's first law of diffusion which states that:

- drug molecules diffuse from a region of higher conc. to lower concentration until equilibrium is attained
- rate of diffusion across a membrane *(dC/dt)* is directly proportional to concentration gradient across the membrane
- rate of passive absorption is proportional to the concentration of absorbable drug in solution in the gi fluids at the site of absorption, hence gastrointestinal absorption of most drugs follows first-order kinetics

Diagram for Passive Transport



$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{D \bullet A \bullet (Ch - Cl)}{x}$$

$$dM/dt = K[C_h - C_l] \text{ where } K = DA/x$$

Rate of diffusion as per Fick's First law

Diffusion coefficient[D]

- Related to size and lipid solubility of drug & viscosity of the diffusion medium.
- As lipid solubility increases or molecular size decreases then D increases and thus dM/dt also increases.

Surface area[A].

- As the surface area increases the rate of diffusion increases.

Compare rate of drug absorption from intestine with that from stomach. Is there any difference in absorption rate? Why?

Membrane thickness [x]. The smaller the membrane thickness the quicker the diffusion process.

dC/dt is the rate of appearance of drug in the blood from the site of absorption

Concentration difference [C_l - C_h]

- Drug concentration in blood or plasma is quite low compared with that of git concentration
- It is this concentration gradient which allows the rapid complete absorption of many drug substances
- Normally, if $C_l << C_h$ then

$$\frac{dM}{dt} = -\frac{D \bullet A \bullet Ch}{x}$$

constant, ka

Sink condition

Implications of sink condition

- ❖ It represents first-order kinetics : $dm/dt = K_a m_t$
  - ➢ the instantaneous rate at which the concentration of drug diminishes in the site of absorption is at any moment proportional to the remaining concentration of the drug in the site of absorption [‘m’ is diffusible mass at time ‘t’]
- ❖ It positively impacts on the extent of absorption
  - ➢ Since it helps sustaining a concentration gradient & thus favours a complete absorption of the administered dose

Note: There are some conditions for which sink condition may not apply& hence extent of absorption is declined

For instance, during physical exercise, viscera perfusion is reduced, negatively impacting on bioavailability of some less permeable drugs

Generalized facts about passive diffusion :

- Down hill transport
- The greater the surface area & lesser the membrane thickness, the faster the diffusion.
- Equilibrium is attained when the concentration on both sides of the membrane becomes equal.
- The greater the membrane/water partition coefficient of a drug, the faster the absorption.
- Passive diffusion process is energy independent but depends more or less on the square root of the molecular size of the drugs.
- The mol. Wt. of most drugs lie between 100 to 400 Daltons which can be effectively absorbed passively.

2.Carrier mediated transport mechanism

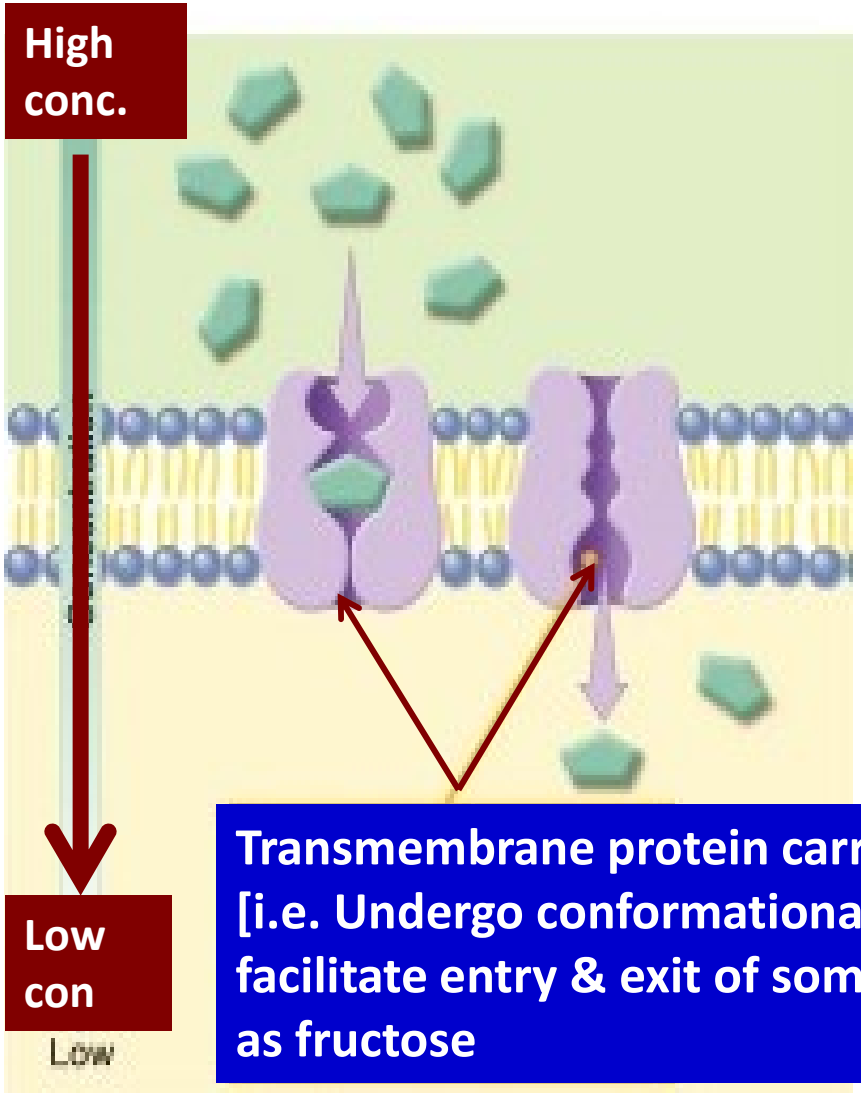
- Involves a carrier (a component of the membrane) which binds reversibly with the solute molecules to be transported to yield the carrier solute complex which transverses across the membrane to the other side where it dissociates to yield the solute molecule
- The carrier then returns to its original site to accept a fresh molecule of solute.
- The carrier-mediated membrane transporters in the small intestine include the peptide transporters, the nucleoside transporters, the sugar transporters, the bile acid transporters, the amino acid transporters, the organic anion transporters and vitamin transporters

Drug transporters	Examples of drugs
Peptide	**Penicillins, cephalosporins, ACE inhibitors and renin inhibitors**
Nucleoside	**Antiretroviral and anticancer drugs**
Amino acids	**L-dopa and methyldopa**

Types of carrier mediated transport system:

1. Facilitated diffusion [passive-mediated transport]
2. Active transport

Facilitated diffusion

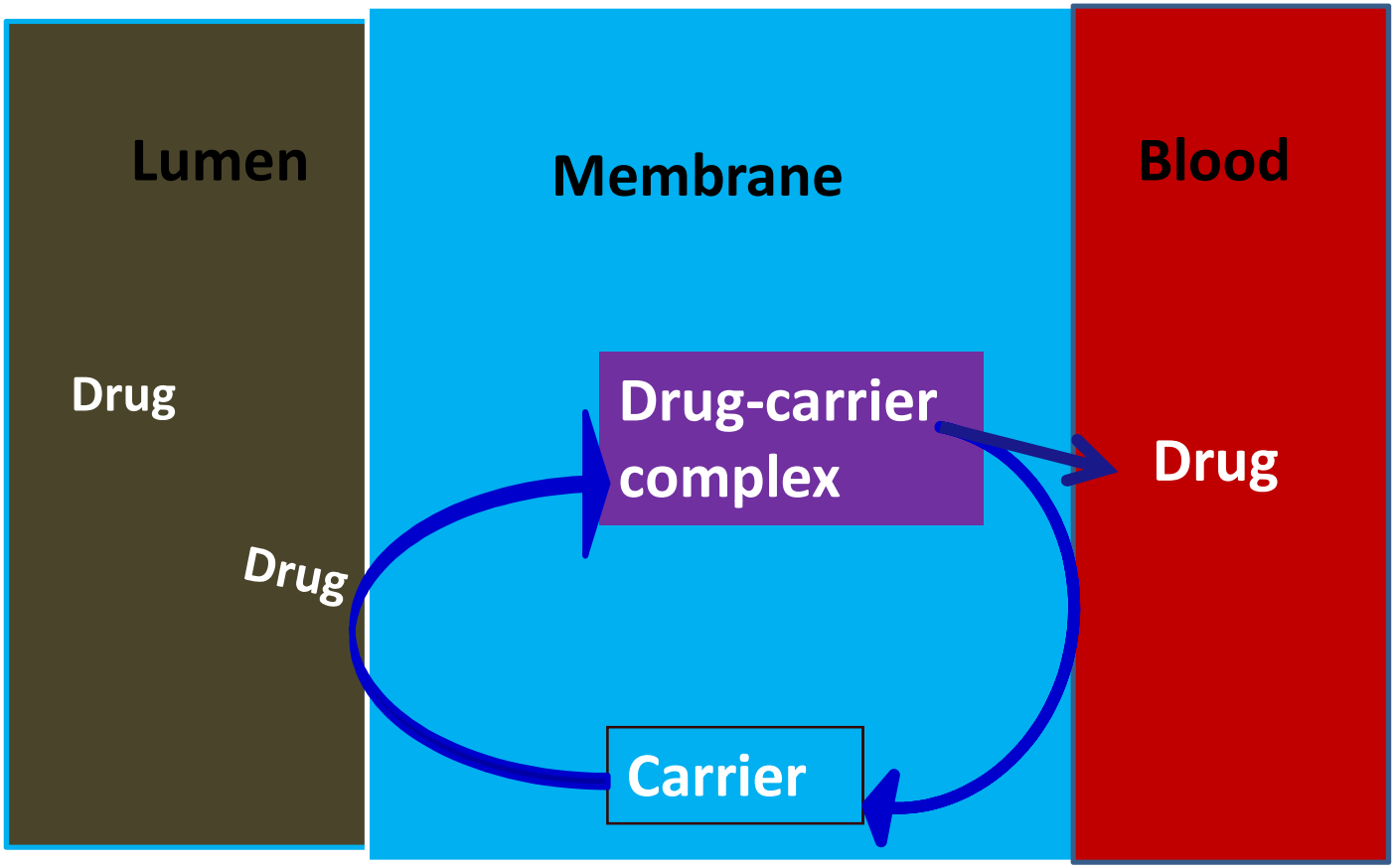


Transmembrane protein carrier changes shape [i.e. Undergo conformational changes] to facilitate entry & exit of some nutrients such as fructose

- Driving force is concentration gradient
- No expenditure of energy [down-hill transport]
- It is not inhibited by metabolic poisons that interfere with energy production. Why??

Example: Vitamin B-12

Facilitated diffusion from lumen to blood across membrane



Note: Drug molecules can be transported via **protein channel** formed by transmembrane integral protein that crosses lipid bilayer or passes between adjacent cells] and **carrier molecules** inherent to biological membrane & undergo conformational change whenever it forms drug-carrier complex

Active transport

- More important process than facilitated diffusion
- The driving force is against the concentration gradient or uphill transport requiring energy expenditure
- Can be inhibited by metabolic inhibitors [poisons] such as dinitrophenol, sodium fluoride, cyanide as they interfere with energy production
- Show temperature dependence
- Can be competitively inhibited by substrate analogues

Example: Active transport based absorption of levodopa is impaired via competitive inhibition when ingested with proteinous meals

- Saturable
- Plays an important role in the intestinal, renal and biliary excretion of many drugs

Note:

1. Simple diffusion based rate of drug absorption can be modeled by Fick's first law:

$$\frac{dM}{dt} = -DA[C_H - C_l]/x$$

2. In contrast, carrier mediated transport based rate of drug absorption can be modeled by Michaelis-Menten kinetic equation:

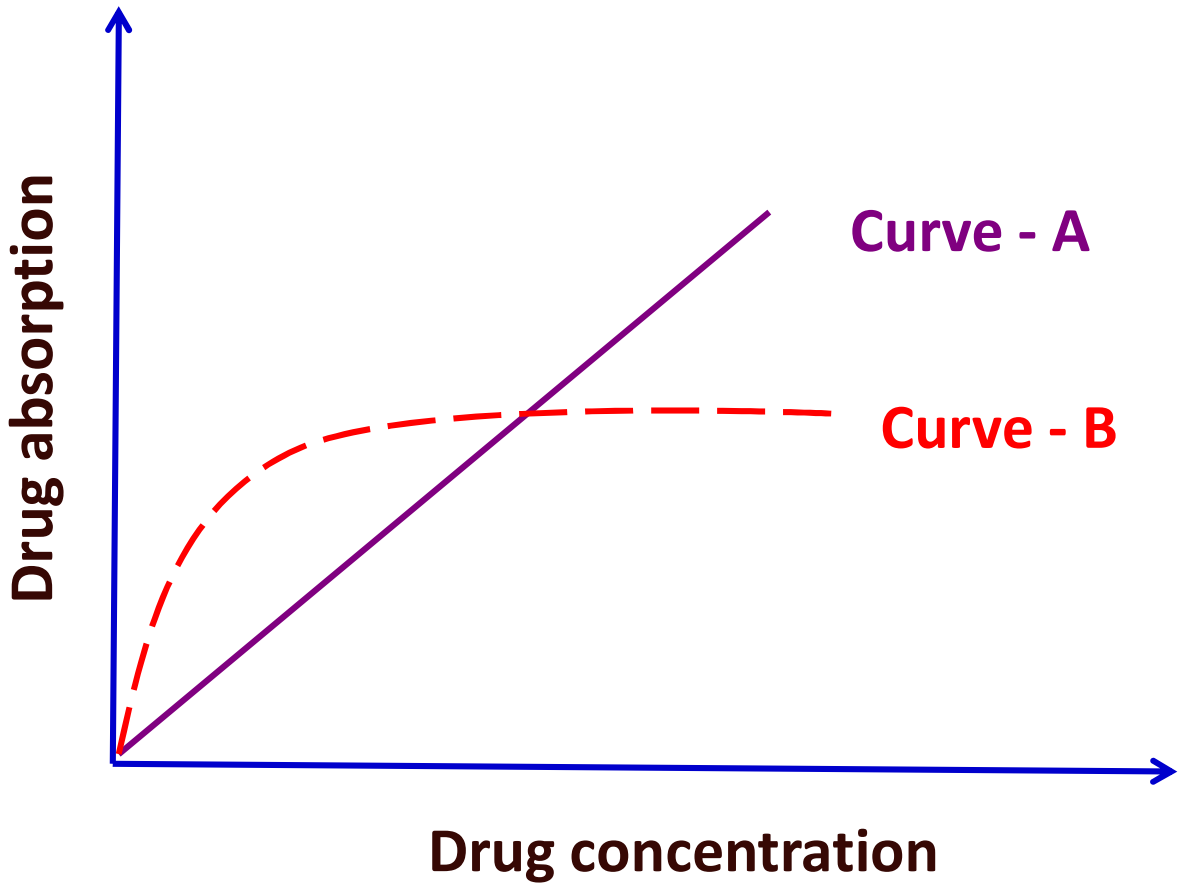
$$\frac{dc}{dt} = \frac{[C].(dc/dt)max}{Km + [C]} = \frac{[C].\ V_{max}}{Km + [C]}$$

Where,

(dc/dt)max = maximal rate of drug absorption at high [drug]

[C] = concentration of drug available for absorption

Km = affinity constant of drug for the barrier.



Relationship b/n drug concentration & absorption rate for passive [Curve A] and carrier-mediated process[curve B]

3.Ionic or electrochemical diffusion

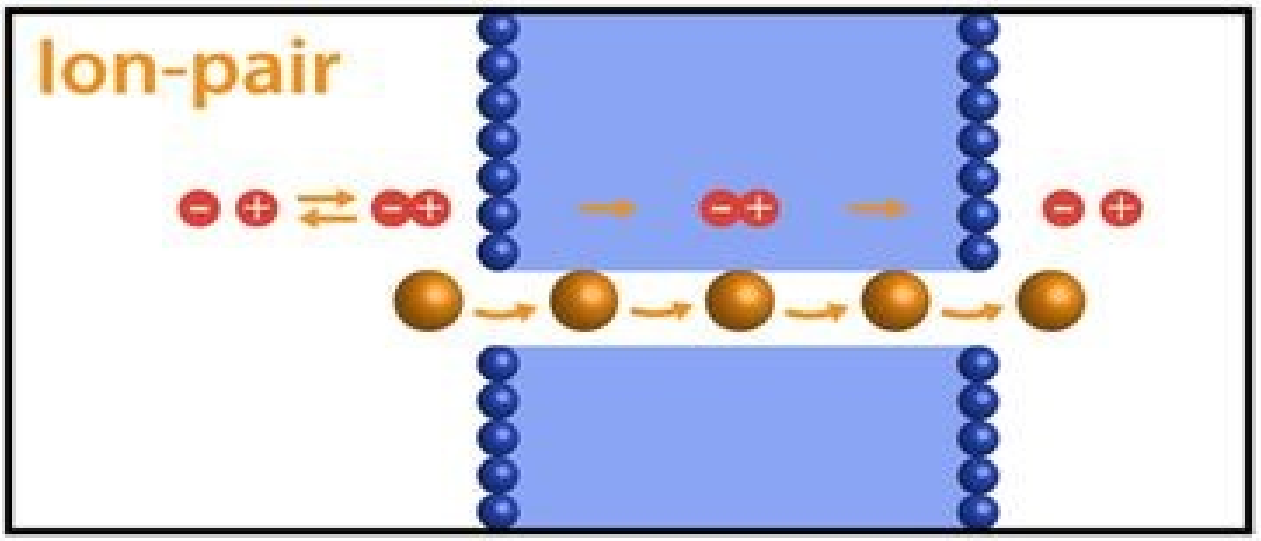
- Permeation of drug is influenced by charge
- Molecular forms of solutes are unaffected by the membrane charge & permeate faster than ionic forms.
- The permeation of anions & cations is influenced by pH
- Thus, at a given pH, the rate of permeation may be as follows:

Unionized molecule > **cations**> **anions**

- The permeation of ionized drugs, particularly the cationic drugs, depend on the potential difference or electrical gradient as the driving force across the membrane.
- Once inside the membrane, the cations are attached to negatively charged intracellular membrane, thus giving rise to an electrical gradient.
- If the same drug is moving from a higher to lower concentration, i.e., moving down the electrical gradient , the phenomenon is known as electrochemical diffusion

4.Ion pair transport

- Strong electrolyte drugs or charged molecules, such as quaternary nitrogen compounds penetrate membranes poorly.
- When such drugs are linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral.
- Such neutral complex diffuses more easily across the membrane

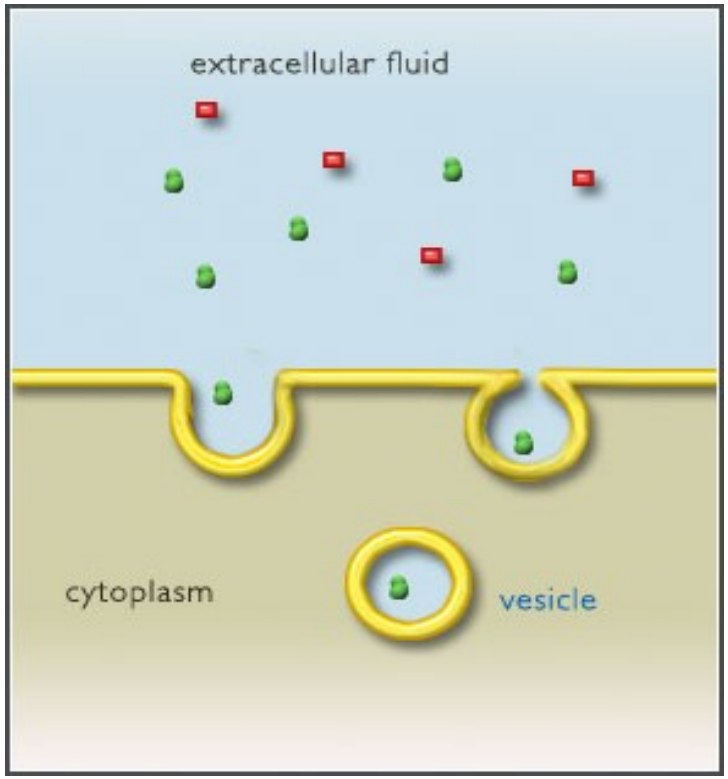

Ion-pair

- Drugs which have low o/w partition coefficient values penetrate the membrane by forming reversible neutral complexes with endogenous ions

  e.g. Mucin of GIT.

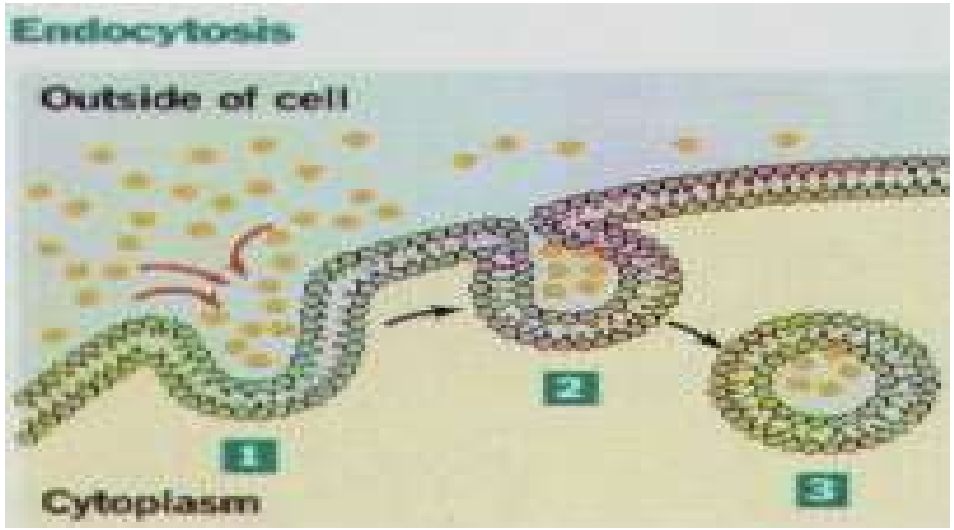
- Such neutral complexes have both the required lipophilicity as well as aqueous solubility for passive diffusion.

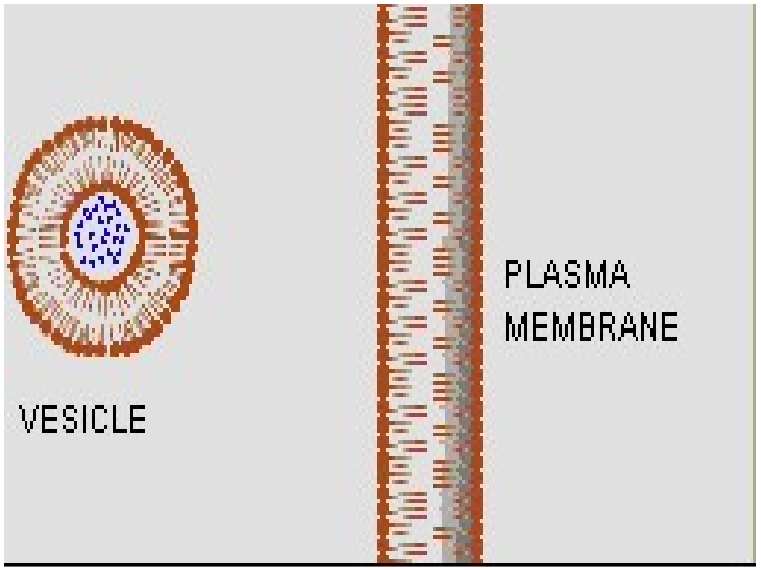
5.Endocytosis



- Involves engulfing extracellular materials within a segment of the cell membrane to form a vesicle which is then pinched off intracellularly
- The uptake process is energy dependent
- Thought to be the primary mechanism of transport of macromolecules

Endocytosis





Types of endocytosis:

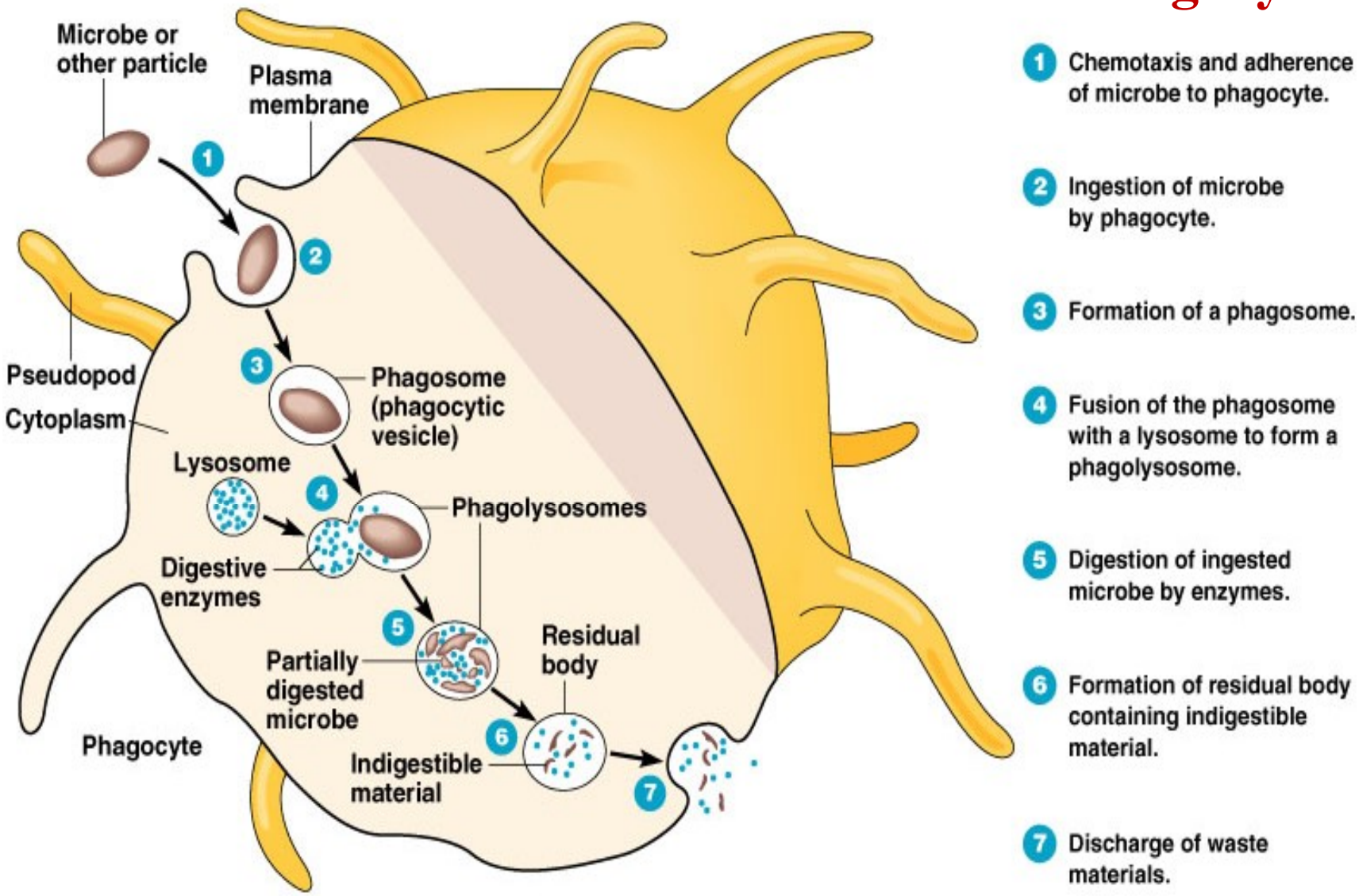
A) Phagocytosis [vital for vaccine &polio absorption from git]

B) Pinocytosis [Fluid-phase endocytosis]

C) Receptor-mediated endocytosis

C) Transcytosis

A. Phases of Phagocytosis



(a) Phases of phagocytosis

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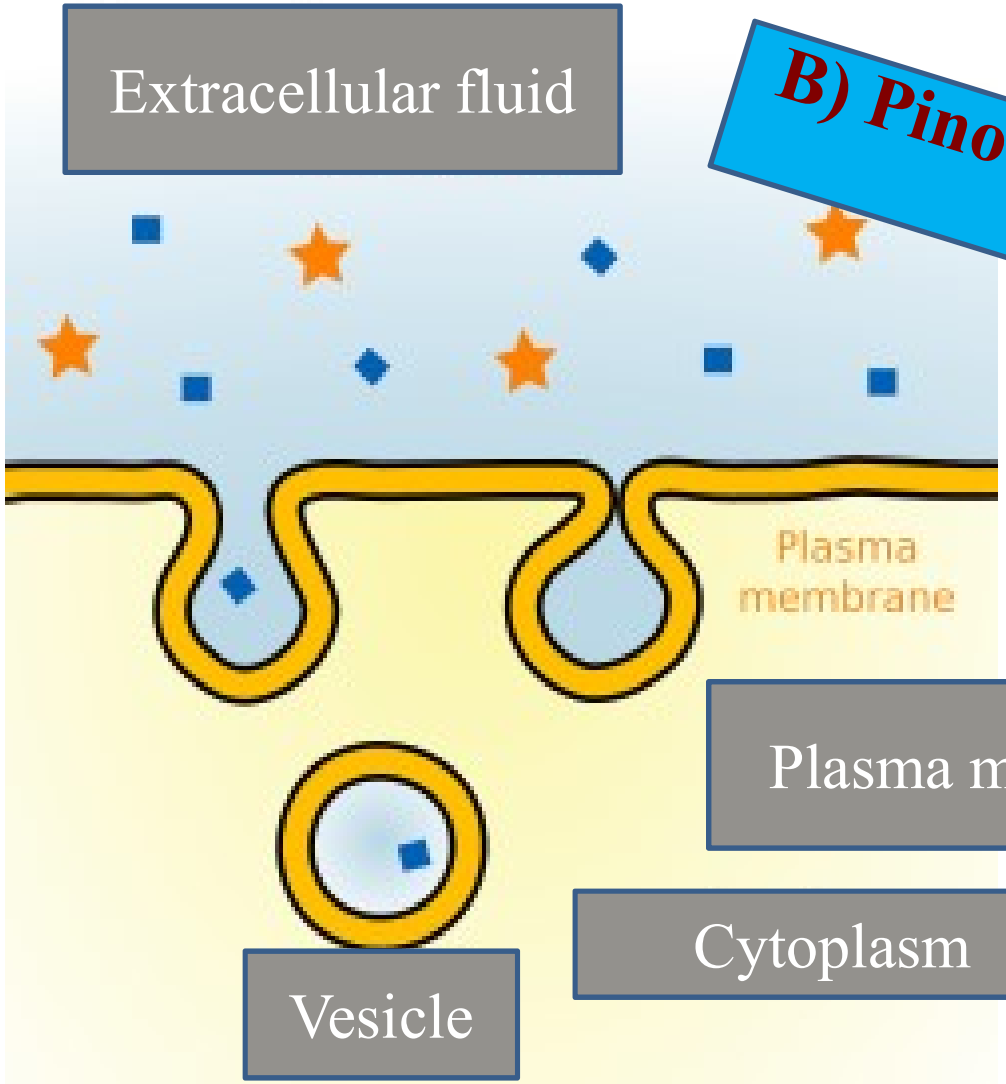
B) Pinocytosis

- Important for absorption of fat soluble vitamins & nutrients

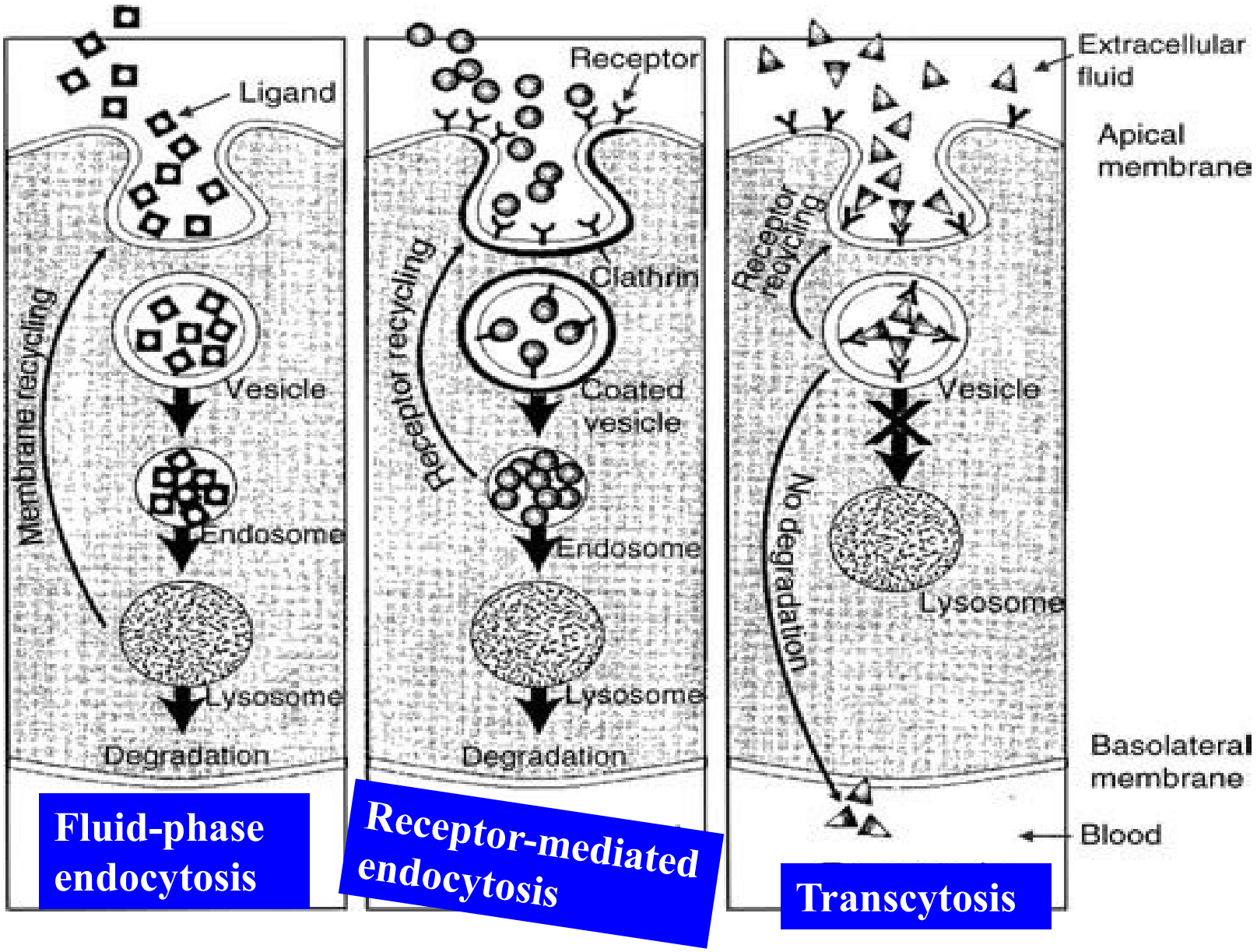


C. Receptor-mediated endocytosis

- Receptor on the cell surface bind with ligand to form ligand-receptor complex
- Complex formation triggers conformational change in the membrane such that the complex invaginates and breaks off from the membrane to form coated vesicles
- Once the coated vesicle is in the cytoplasm, it become uncoated and deliver its contents to endosomes where ligand-receptor complex is dissociated
- The free ligand is transferred to lysosomes where it is digested by lysosomal digestive enzymes

D. Transcytosis: The process by which the material is internalized by the membrane domain & transported through the cell and secreted on the opposite side

- Transcytosis rate depends on polarity and size.
  - ➢ The greater the lipid solubility the faster the rate of diffusion
  - ➢ Large polar molecules[sugar, aa, phosphorylated] have slow rate of diffusion


Ligand
Membrane recycling
Vesicle
Endosome
Lysosome
Degradation
Fluid-phase endocytosis
Receptor
Receptor recycling
Clathrin
Coated vesicle
Endosome
Lysosome
Degradation
Receptor-mediated endocytosis
Extracellular fluid
Apical membrane
Receptor recycling
Vesicle
No degradation
Lysosome
Basolateral membrane
Blood
Transcytosis

Paracellular pathway[PP]

- Transport of materials in the aqueous pores between the cells rather than across cells
- The cells are joined together via closely fitting tight junctions on their apical side thus, the junctions act as a gate & fence to control intercellular molecules movement
- Tight junction is the primary barrier to paracellular transport
- Decreases in importance down the length of the **git** as the number & size of pores b/n epithelial cells decrease
- Important for the transport of ions, sugars, amino acids & peptides at conc. above the capacity of their carriers.
- Small hydrophilic & charged drugs cross gastrointestinal epithelium via the paracellular pathway

- The paracellular pathway can be divided into a convective ('solvent drag') and diffusive component
- Convective component is the rate at which compound is carried across the epithelium via the water flux

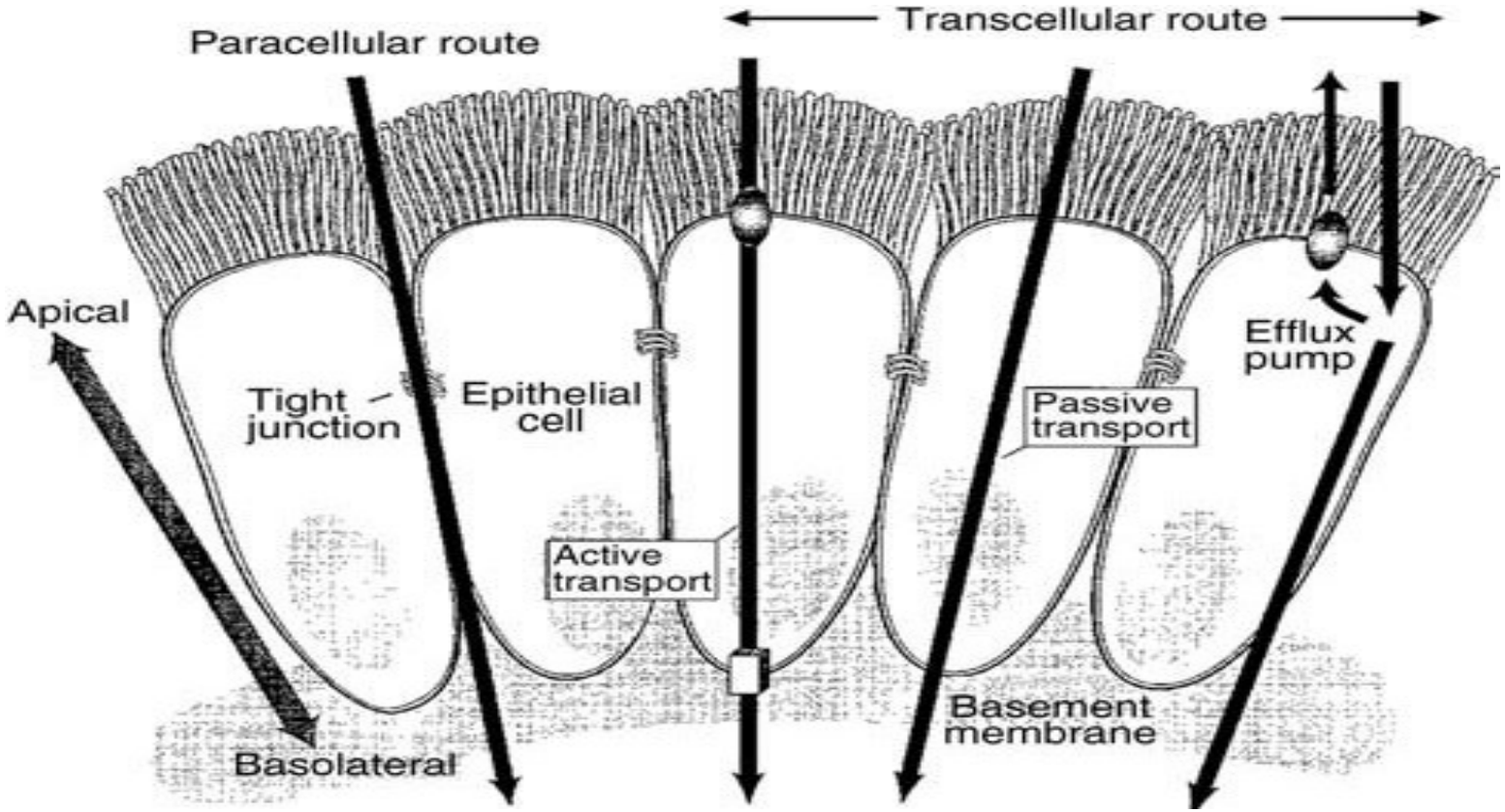


Table 16.2 Examples of transport mechanisms of commonly used drugs across the gastrointestinal absorptive epithelia (adapted from Brayden 1997)

Route	Examples	Therapeutic class
Transcellular passive diffusion	Propranol	β-Blocker
	Testosterone	Steroid
	Ketoprofen	Non-steroidal anti-inflammatory
	Cisapride	Antispasmodic
	Oestradiol	Sex hormone
	Naproxen	Non-steroidal anti-inflammatory
Paracellular	Cimetidine	H_2 antagonist
	Loperamide	Antidiarrhoeal
	Atenolol	β-Blocker
	Mannitol	Sugar used as paracellular marker
	Tiludronate	Bisphosphonate
Carrier mediated	Cephalexin	Anti-bacterial
	Captopril	ACE inhibitor
	Bestatin	Anticancer
	Levodopa	Dopaminergic
	Foscarnet	Antiviral
Transcellular diffusion subject to P-glycoprotein efflux	Cyclosporine	Immunosuppressant
	Nifedipine	Calcium channel blocker
	Verapamil	Calcium channel blocker
	Paclitaxel	Anticancer
	Celiprolol	β-Blocker
	Digoxin	Cardiac glycoside

Pore transport [**convective** transport, bulk flow or filtration]

- It is a paracellular transport
- Important in the absorption of low mol. Wt. (less than 100).
- Low molecular size (smaller than the diameter of the pore) & generally water-soluble drugs are transported through narrow, aqueous filled channels or pores in the membrane structure, example: urea, water & sugars.
- Hydrostatic or osmotic pressure difference across the membrane is the driving force for the passage of drugs

- Rate of absorption via pore transport depends on the number & size of the pores as shown below:

$$\frac{dc}{dt} = \frac{N.A.R^2.\Delta C}{(\eta)(h)}$$

where,

$\frac{dc}{dt}$ = rate of the absorption

N = number of pores

A = Absorptive area

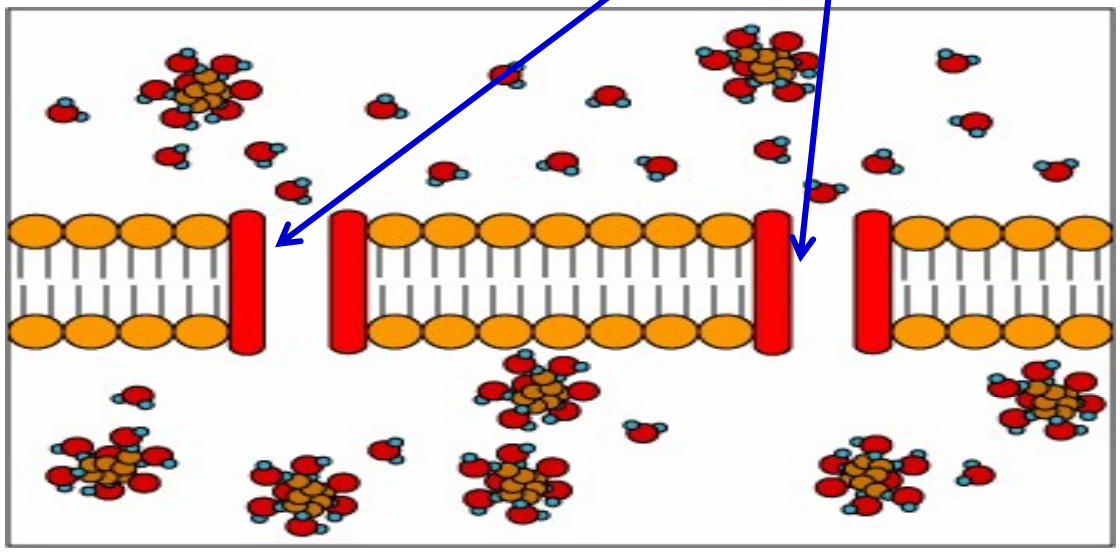
R = radius of pores

ΔC = concentration gradient

η = viscosity of fluid in the pores

h = membrane thickness

Transport via Channel Proteins

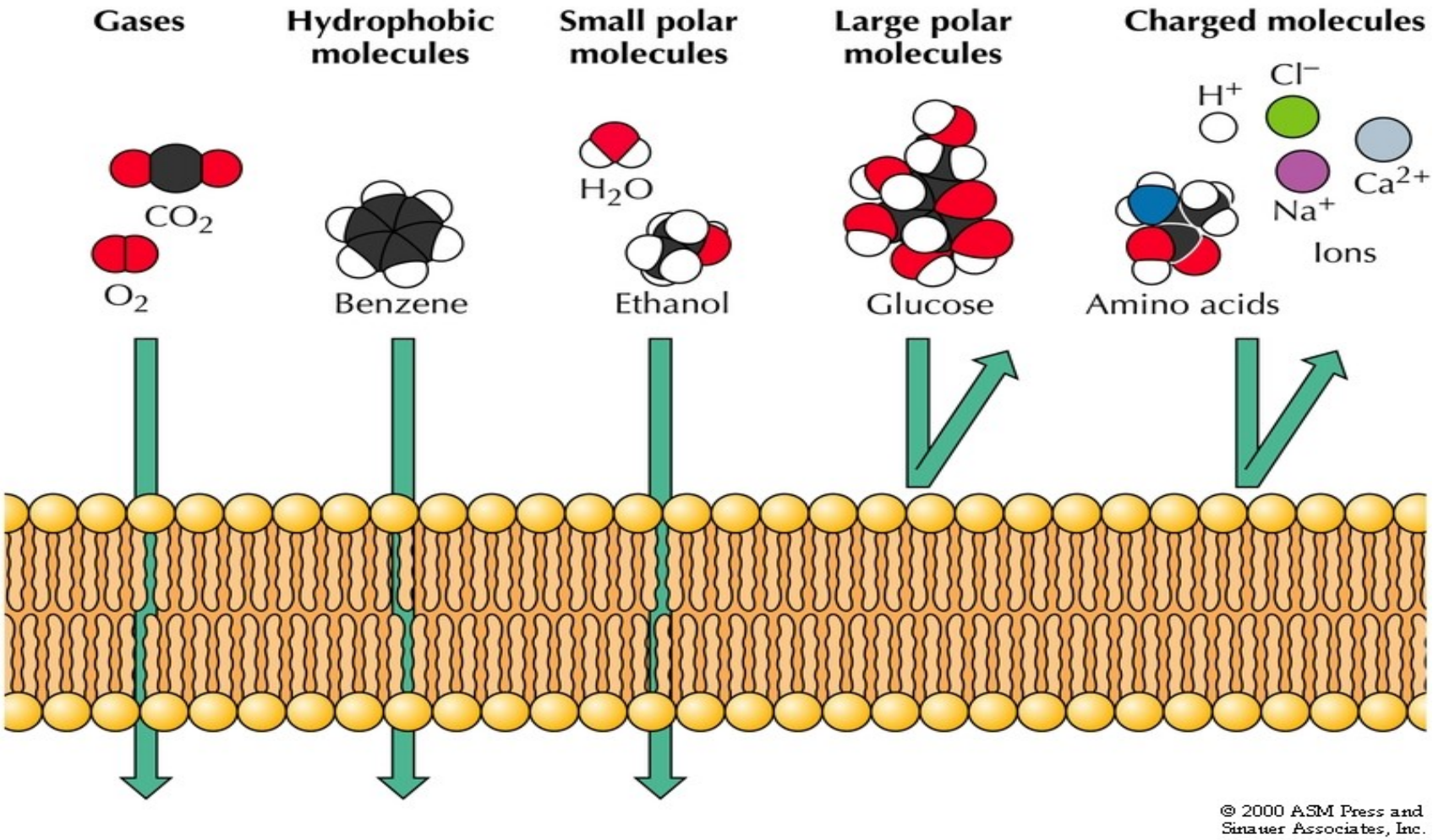


7. P-glycoprotein transport [Counter transport]

- P-glycoproteins(PGP) are present throughout the body including liver, brain, kidney & intestinal epithelia
- Act as reverse pump generally inhibiting absorption or intracellular drug accumulation
- Pump anticancer drug from inside the cell decreasing their intracellular conc., hence causing multidrug resistance in tumour cells
- It is an active, ATP-dependent process, operating against concentration gradient
- Competitively inhibited by structural analogues or by inhibitors of cell metabolism, & is a saturable process

Drug resistance vs PGP???

Summary of movement of substances across cell membranes



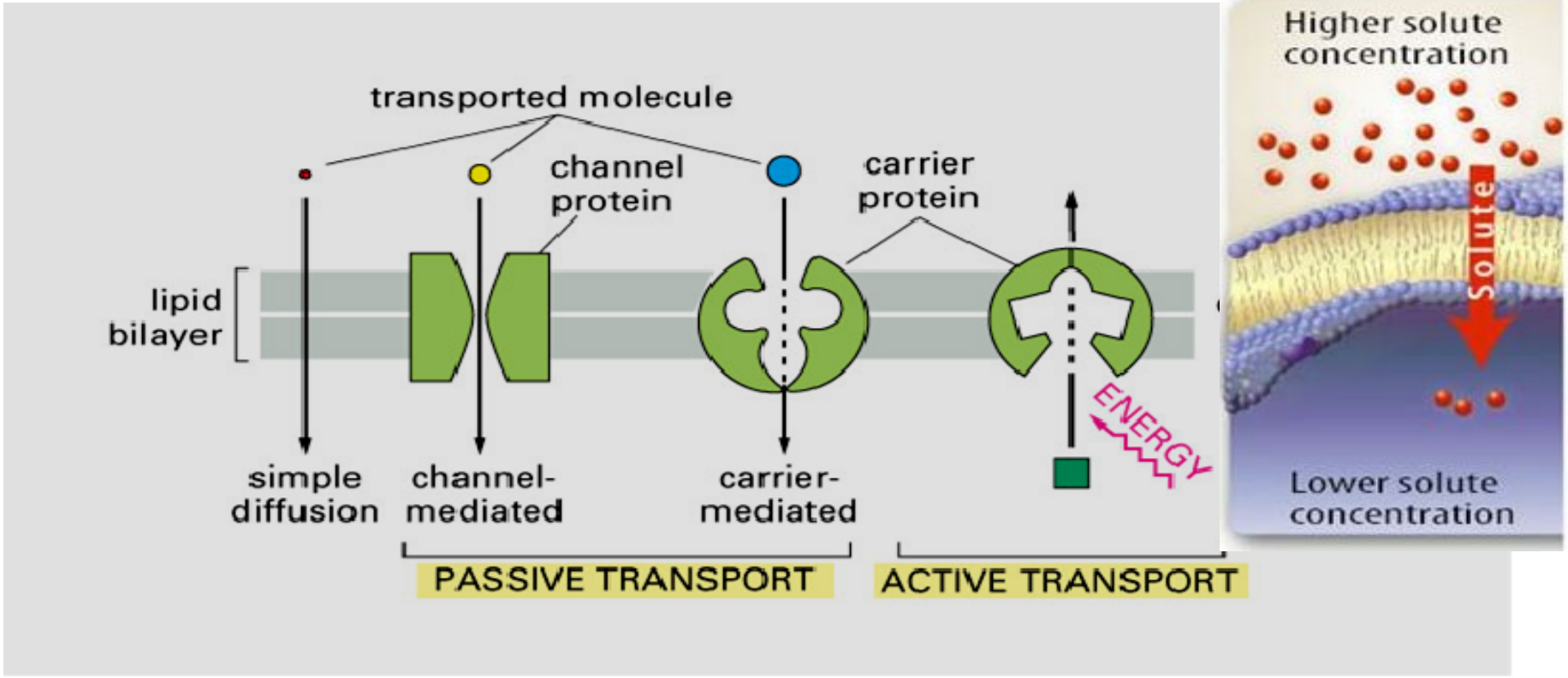


Illustration of Different Transport Mechanisms

Diffusion

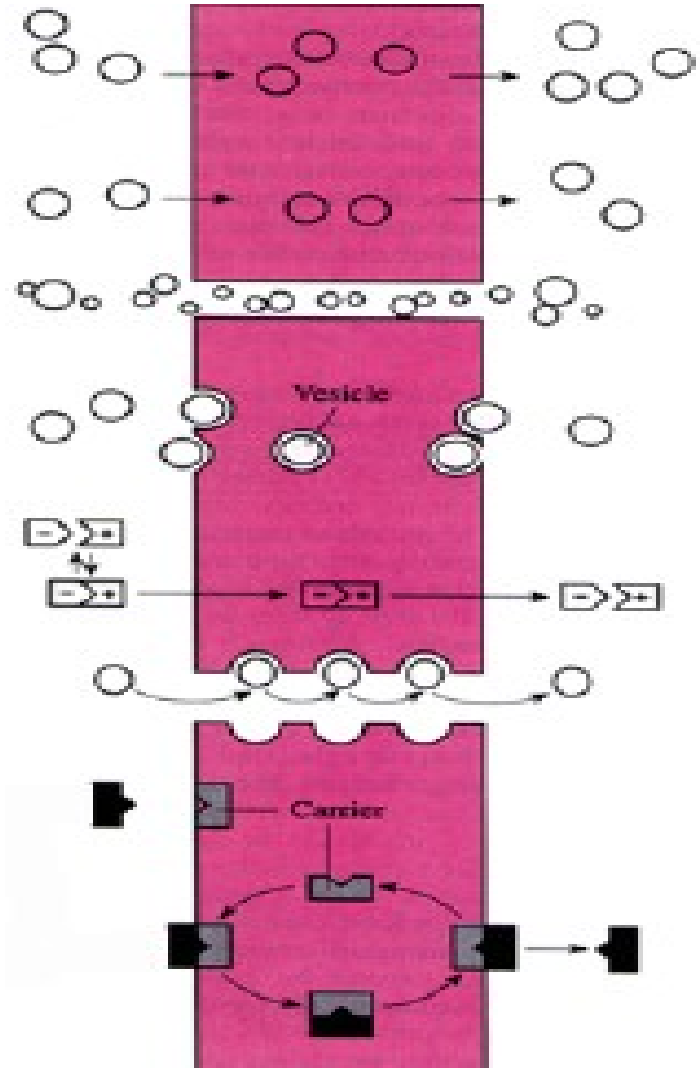
Bulk Flow

Endocytosis

Ion Pair

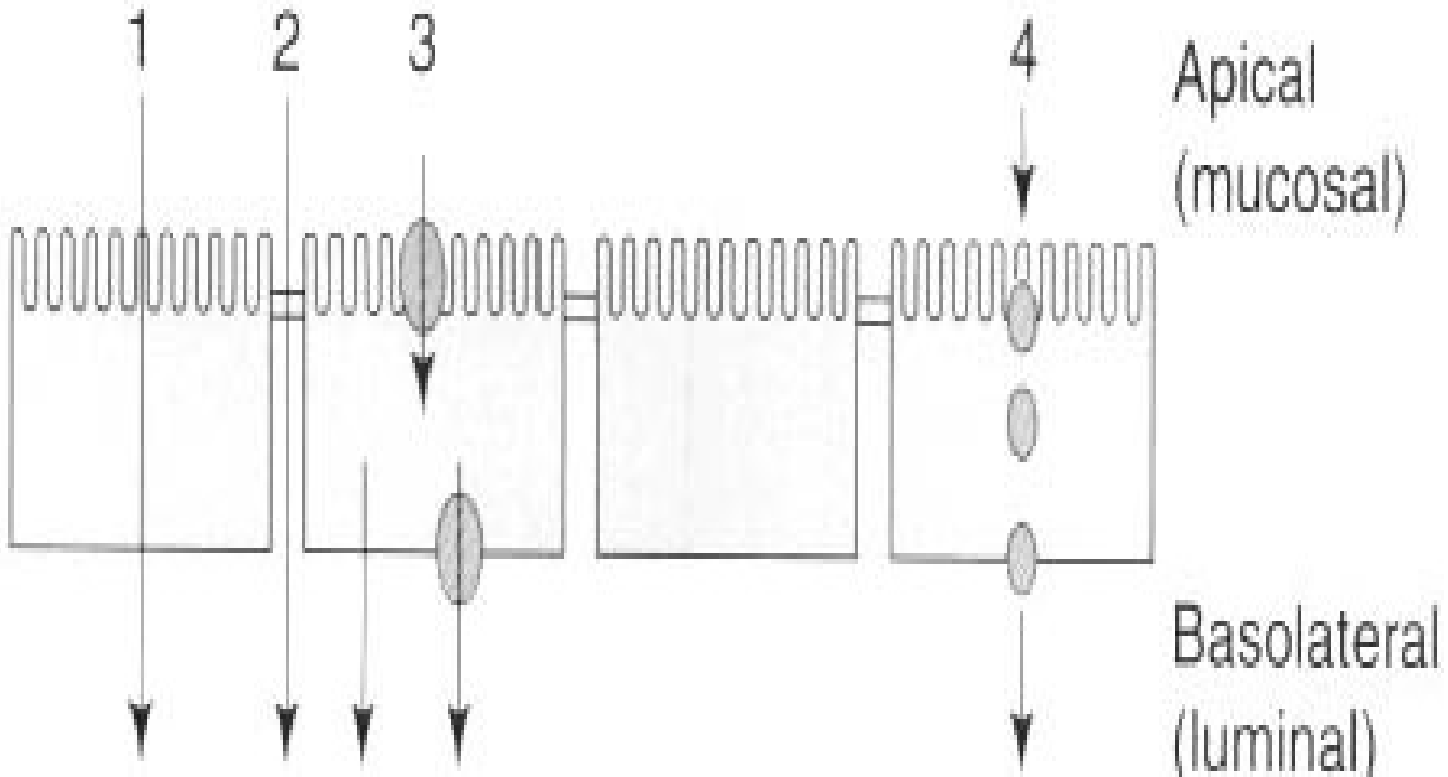
Facilitated Transport

Active Transport



Sugars, amino acids, vitamins

Mechanisms of permeability (absorptive)



1 – Transcellular 3 – Carrier mediated

2 – Paracellular 4 – Transcytosis

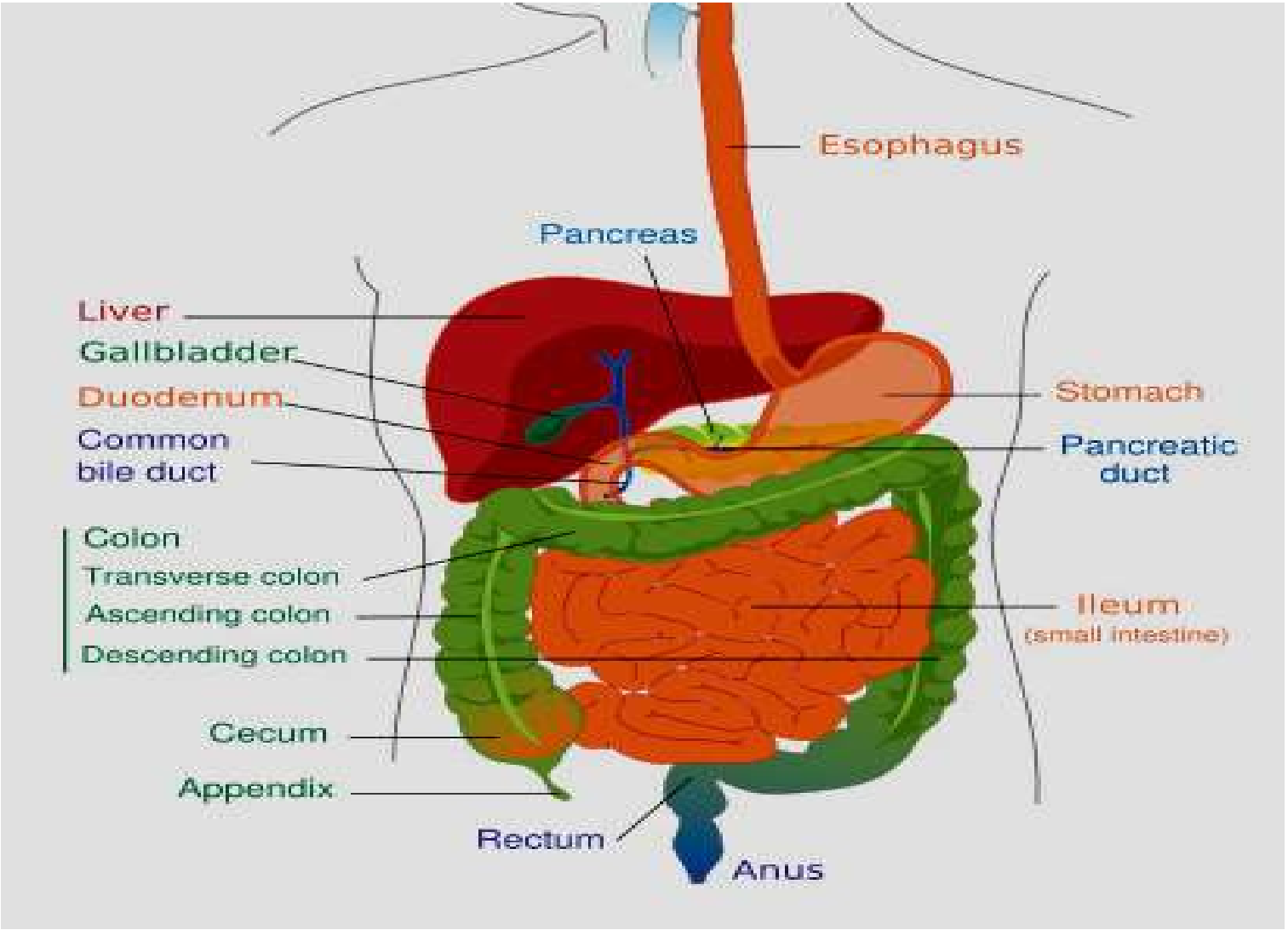
Note

- The ultimate goal of transport of molecules across biological membrane is to have the drug reach the site of action in a concentration that produces a pharmacological effect.

- No matter how the drug is given (other than IV) it must pass through a number of biological membranes before it reaches the site of action

2.1.3. Gastrointestinal physiology

- The gastrointestinal tract is a muscular tube
- GIT stretches from the mouth to the anus
- It is about 6 m in length with varying diameters.
- It consists of four main anatomical areas: the oesophagus, the stomach, the small intestine and the large intestine or colon.
- The majority of the gastrointestinal epithelium is covered by a layer of mucous. This is a Viscoelastic translucent aqueous gel that is secreted through out the GIT, acting as a protective layer and a mechanical barrier. Its main components include mucin [glycoprotein] & water[large proportion]


Esophagus
Pancreas
Liver
Gallbladder
Duodenum
Common
bile duct
Stomach
Pancreatic
duct
Colon
Transverse colon
Ascending colon
Descending colon
Ileum
(small intestine)
Cecum
Appendix
Rectum
Anus

GI physiology that affects drug absorption

A. The environment within the lumen

i. Gastrointestinal pH

- Varies along the length of GIT

  [Alkaline→ Acidic → Alkaline]

- May influence absorption of drugs by affecting:
  - chemical stability of the drug in the lumen

    e.g. Penicillin G, erythromycin
  - drug dissolution or absorption

    e.g. weak electrolyte drug

Note: Following Le Chatelier's principle, in an alkaline media H3O $^{+}$ is consumed up shifting equilibrium to the right & thus increasing concentration of charged species, A^{-}.

Conversely, in acid media equilibrium will shift to left, increasing concentration of non-charged species, HA.

Although, solubility of charged species in aqueous media is higher, their permeability via cell membrane by passive diffusion is lower

Presence or absence of interacting drugs	AUC0–24 (µM h)	Cmax (µM)	Tmax (h)
Atazanavir administered alone	16.3 ± 9.0	3.2± 1.7	2.8 ± 0.75
Atazanavir administered after lansoprazole	0.85 ± 1.8	0.13 ± 0.19	3.1± 1.0

Note:Lansoprazole **decreased** atazanavir AUC by 94%

Mean ± SD

ii. Luminal enzymes

- The primary enzyme found in gastric juice is pepsin.
- Pepsins and proteases are responsible for the digestion of protein and peptide drugs in the lumen.

Think of oral insulin. Is it possible ?? Why?

- Lipases, amylases and proteases are secreted from the pancreas into the small intestine.
- Lipases may affect release of drugs from fat / oil containing dosage forms. How?

What is the rout of absorption of fatty substances?

- Colonic bacteria secrete enzymes that are capable of a range of reactions to cause release of active agent

Examples:

1. Targeting sulphasalazine to colon.

Note: 5-aminosalycylic acid [5-ASA] is used to treat inflammatory bowel disease

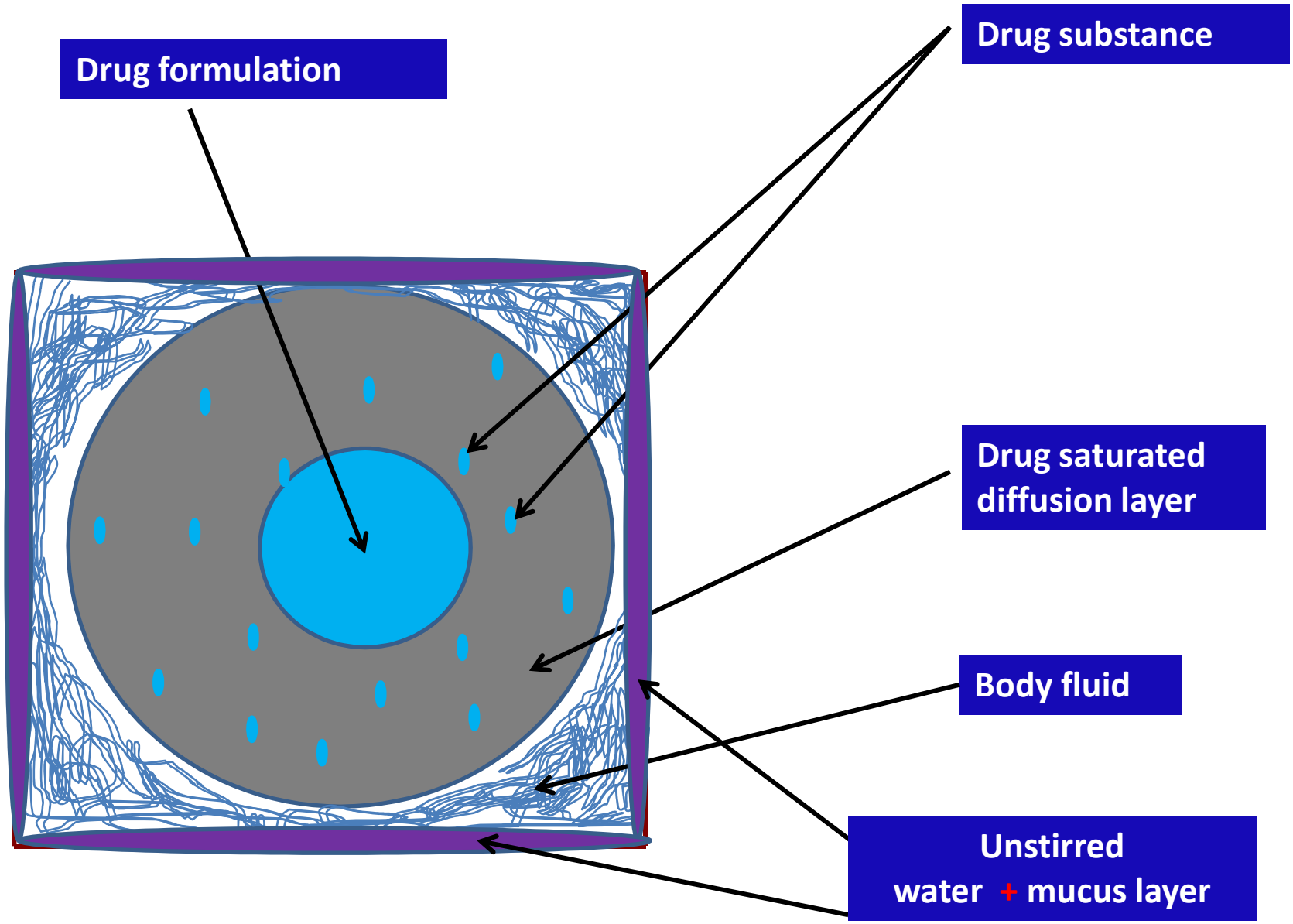
2. Colon drug targeting using β-Cyclodextrin drug complex.

Why targeting ?

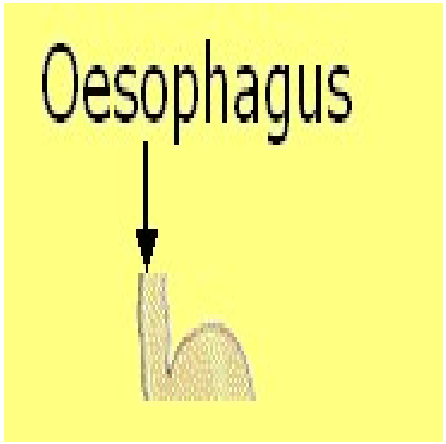
iii. The unstirred water layer

- It is a layer of water and mucous adjacent to the intestinal wall.
- It is a more or less stagnant layer as it involves laminar but not turbulent flow
- This layer can provide a diffusion barrier to drugs.

  Thickness of stagnant layer versus diffusion rate ?
- Some drugs (antibiotics e.g. tetracycline) are capable of complexing with mucous, thereby reducing their availability for absorption→↓rate of drug absorption


Drug formulation
Drug substance
Drug saturated diffusion layer
Body fluid
Unstirred water + mucus layer

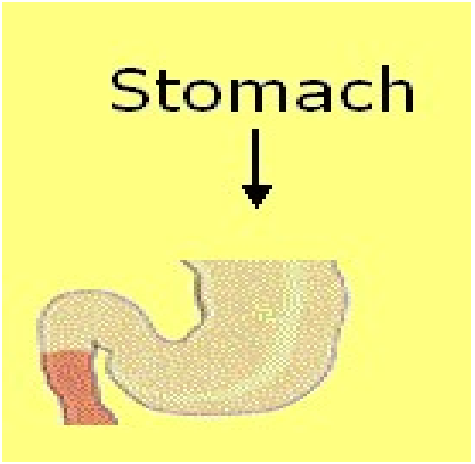
B.Transit of pharmaceuticals in the GIT

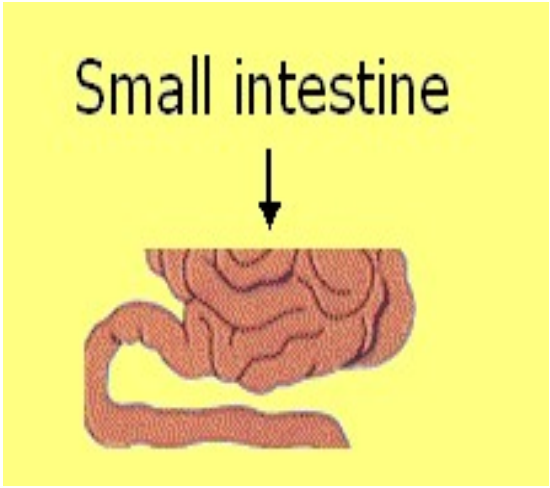


Once a drug is placed in the mouth it is moved down the oesophagus by the swallowing reflex.

The transit time of dosage form in the oesophagus is rapid usually, 10-14 seconds.

The transit time in stomach is highly variable & depends on dosage form & fed or fasted state of the stomach.



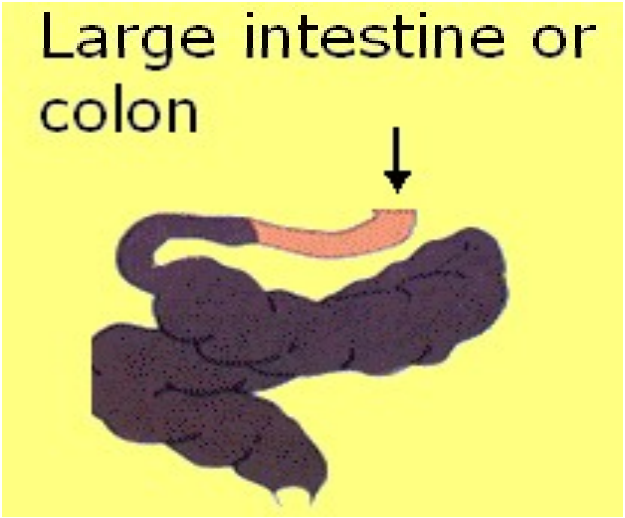


Transit time is:

- relatively constant, at around 3 hours.
- contrasts with stomach as it does not discriminate b/n different dosage forms or b/n fed or fasted state.
- Main site for absorption of most drugs.

Transit time is:

- long and variable
- depends on:
  - ✓type of dosage form
  - ✓ diet
  - ✓eating pattern
  - ✓ disease state



C. Disease state and physiological disorders

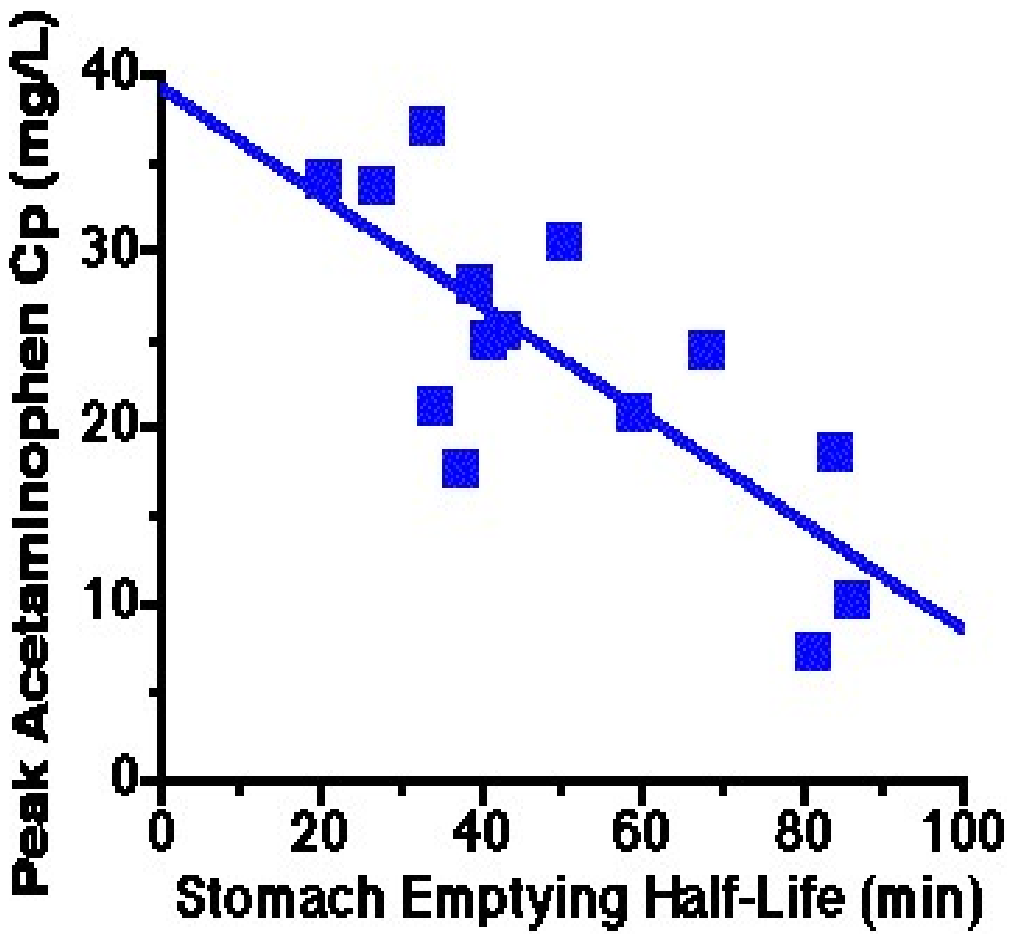
- Local diseases can cause change in gastric pH affecting stability, dissolution & absorption of drug
- Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in normal individuals, resulting in an increased overall rate of absorption of drugs that are absorbed from the SI.
- However, drugs that require a period of time in the stomach to facilitate their dissolution may show reduced bioavailability in such patients

What to be done?

D. Gastric emptying and motility

- The time a dosage form takes to traverse the stomach is usually termed: gastric residence time, gastric emptying time or gastric emptying rate
- Generally drugs are better absorbed in the small intestine than in the stomach, therefore quicker stomach emptying increases drug absorption.
- Slower stomach emptying may cause increased degradation of drugs in the stomach's lower pH

  e.g. L-dopa.
- The quicker the stomach emptying (shorter stomach emptying time) the higher the plasma concentration of acetaminophen .



Peak acetaminophen plasma concentration as a function of stomach emptying half-life

Factors Affecting Gastric Emptying

- Viscosity
  - Rate of emptying is greater for less viscous solutions
- Emotional states
  - Stressful emotional states increase stomach contraction and emptying rate
  - Depression reduces stomach contraction and emptying
- Disease states
  - Rate of emptying is reduced in some diabetic patients, hypothyroidism
  - Rate of emptying is increased in hyperthyroidism
- Exercise
  - Reduce emptying rate

Note: *Exercise reduces gastric emptying rate & hence dereases oral absorption of some drugs such as Sulfadimidine, Sulfaethizole Quinidine & Salicylate*

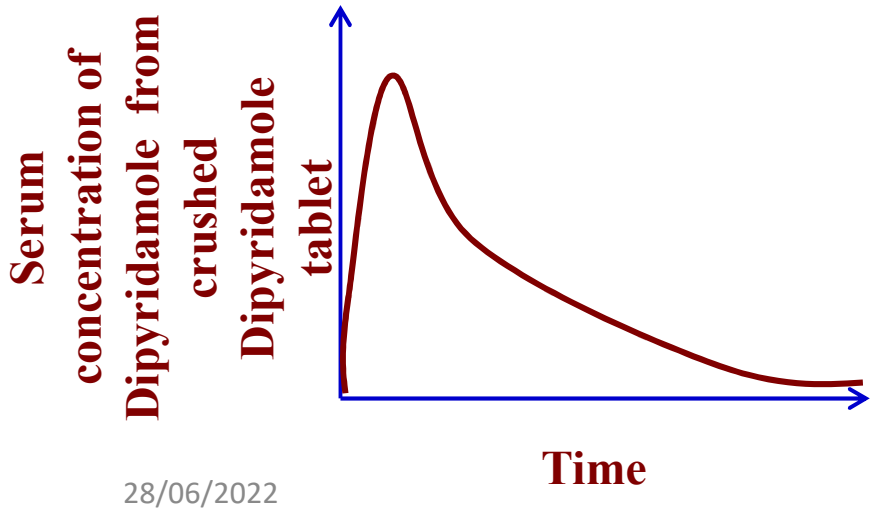
Double-peak phenomenon

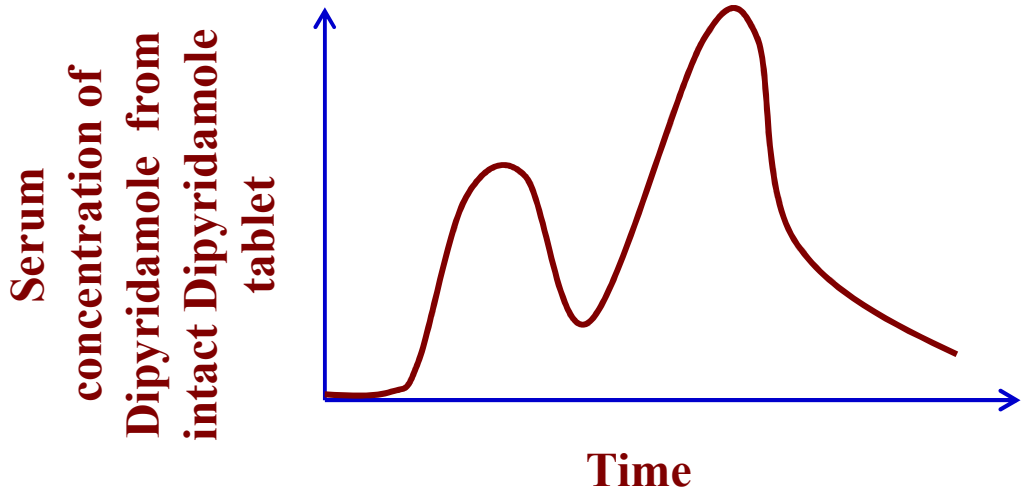
Double peak refers to formation of blood concentration curve consisting of two peaks

Rationale for double-peak phenomenon

- ❖ Variability in stomach emptying
- ❖ Presence of food in the stomach
- ❖ Variable intestinal motility
- ❖ Entero-haepatic recycling

Examples	Reasons for double peak formation following single dose
Cimetidine	Variability in stomach emptying & intestinal flow rates during entire absorption process
Ranitidine[after oral & IV bolus]	Entero-hepatic recycling
Dipyridamole	Tablet integrity & delayed gastric emptying





E. Effect of gastric contents

Food

Presence of food in the GIT can influence rate and extent of drug absorption, directly or indirectly via a range of mechanisms

I . Complexation of drugs with components in diet

Example

Tetracycline forms non-absorbable complexes with calcium and iron, and thus it is advised that patients do not take products containing calcium or iron, such as milk, iron preparations or indigestion remedies concurrently with tetracycline

ii. Alteration of pH

Food tends to increase stomach pH by acting as a buffer. This liable to decrease the rate of dissolution and absorption of a weakly basic drug and increase that of a weakly acidic one. **Why?**

iii. Alteration of gastric emptying

Fats and some drugs tend to reduce gastric emptying rate and thus delay the onset of action of certain drugs

iv. Stimulation of gastrointestinal secretions

- Gastrointestinal secretions (e.g. pepsin) produced in response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism, and hence a reduction in their bioavailability
- Fats stimulate the secretion of bile
- Bile salts are SAA, hence increase dissolution of poorly soluble drugs such as Griseofulvin
- Bile salts can form insoluble and non-absorbable complexes with some drugs, such as Neomycin and Kanamycin

v. Food-induced changes in presystemic metabolism

- Certain foods may increase BA of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process.

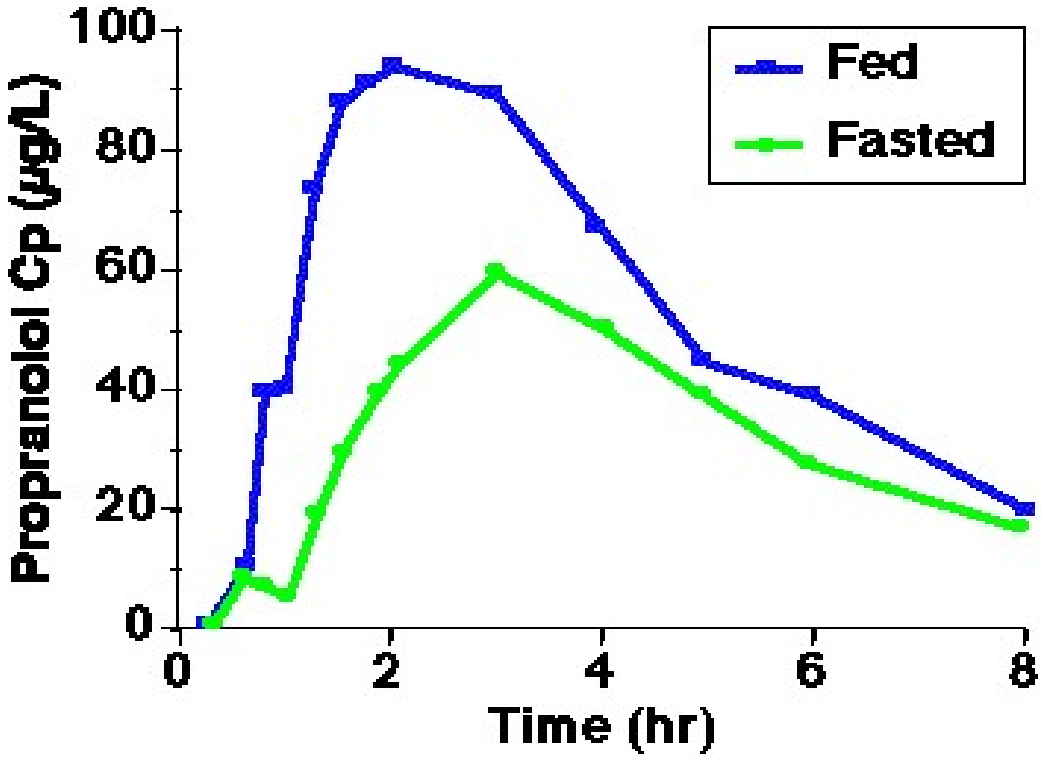
E.g. Grapefruit juice enhances bioavailability of drugs susceptible to CYP_3A by inhibiting the intestinal Cytochrome P_{450}

vi. Food-induced changes in blood flow

- Food serve to increase BA of some drugs that are susceptible to first-pass metabolism , e.g. propranolol.

Is it advisable taking such drug with food ? [Yes/No]. **Why?**

- Blood flow to GIT and liver increases after a meal.
- Faster rate of drug presentation to the liver implies larger fraction of drug escaping first-pass metabolism since enzyme are saturated.



Effect of Fasting *versus* Fed on Propranolol Concentrations

F. Presystemic drug metabolism

Definition

Metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of amount of unmetabolized drug reaching systemic circulation.

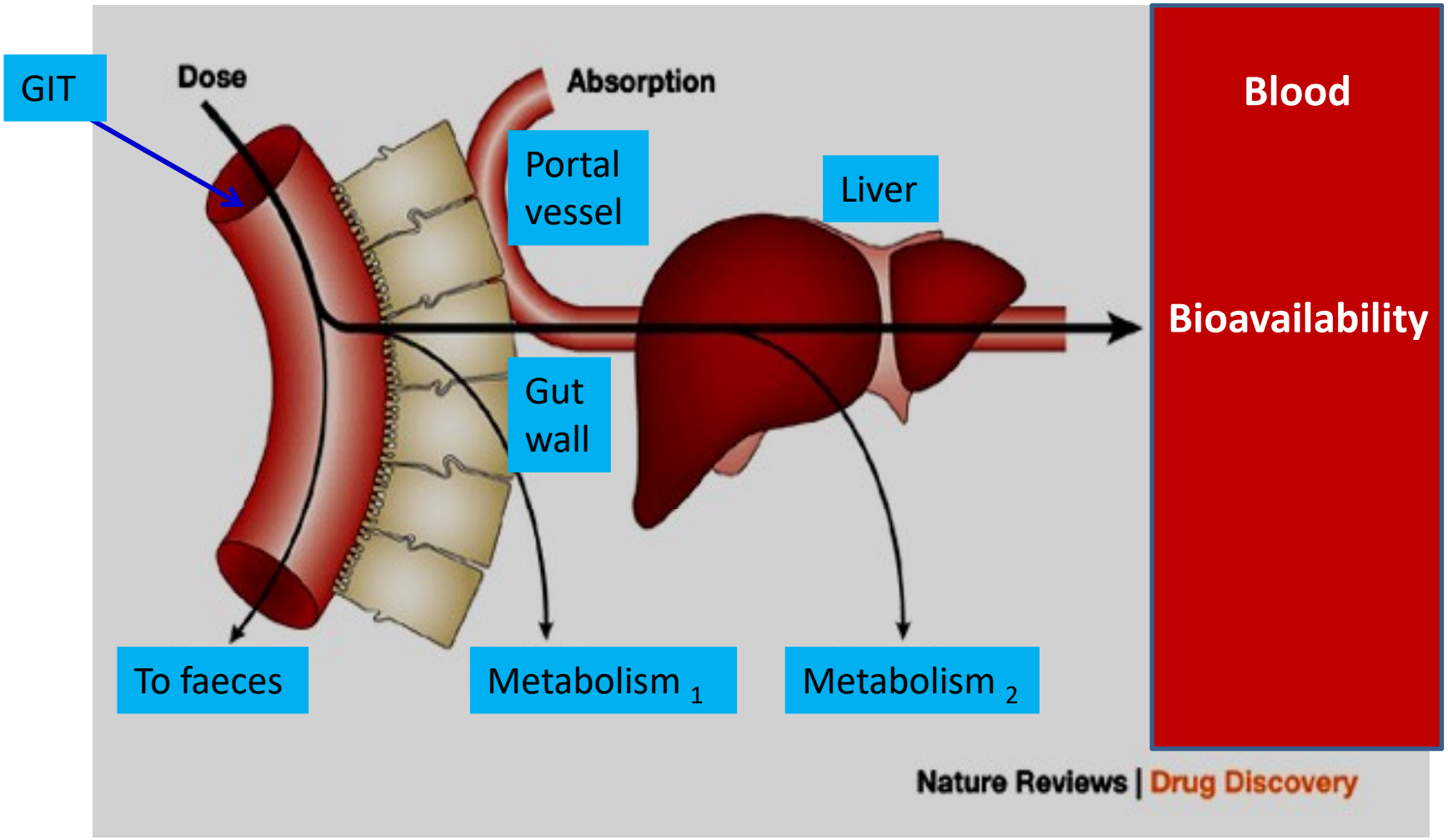
A. Gut wall metabolism

- is known as first-pass metabolism by the intestine.
- Cytochrome P450 enzyme, CYP3A, that is present in the liver and responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and that intestinal metabolism may be important for substrates of this enzyme

  e.g. cyclosporine

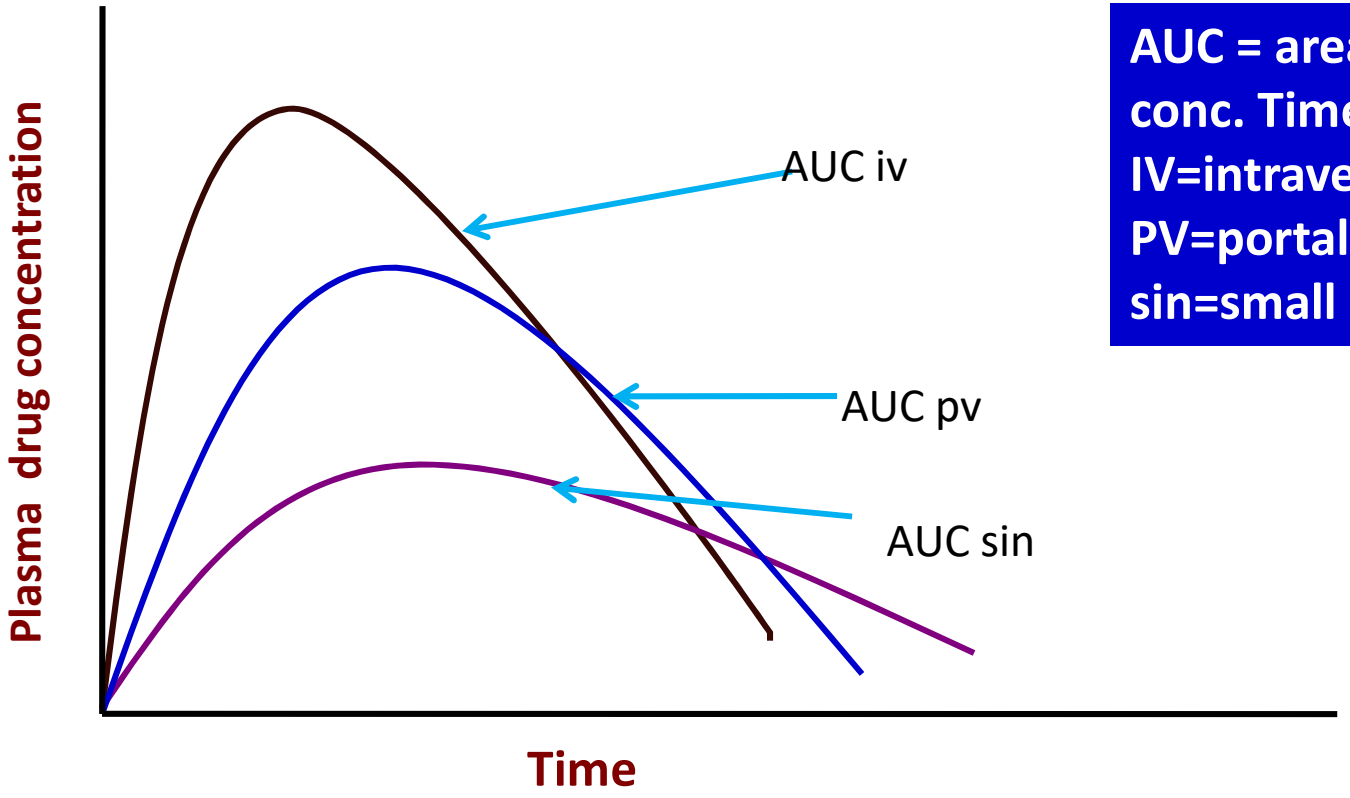
B. Hepatic metabolism

- Drugs absorbed from the digestive system enters the hepatic portal system.
- It is carried through the portal vein into the liver before it reaches the rest of the body.
- The liver metabolizes many drugs (e.g. propranolol), sometimes to such an extent that only a small amount of active drug,30% of oral dose emerges from the liver to the rest of the circulatory system
- Tricyclic antidepressant imipramine & analagesic pentazocine are rendered to *first pass* so that their bioavailability is greatly reduced



Presystemic drug metabolism = Metabolism $_1$ + Metabolism $_2$

Comparison of drug availability after Presystemic metabolism



AUC = area under conc. Time curve, IV=intravenous, PV=portal vein, sin=small intestine

2.2. Physico-chemical factors affecting drug absorption

A. Particle size : Affects absorption of drugs with low aqueous solubility

- Absorption of such drugs is increased via *Micronization*

Micronization → ↑ surface area → ↑ dissolution rate → faster rate of absorption

- Micronization also reduces dose of some drugs

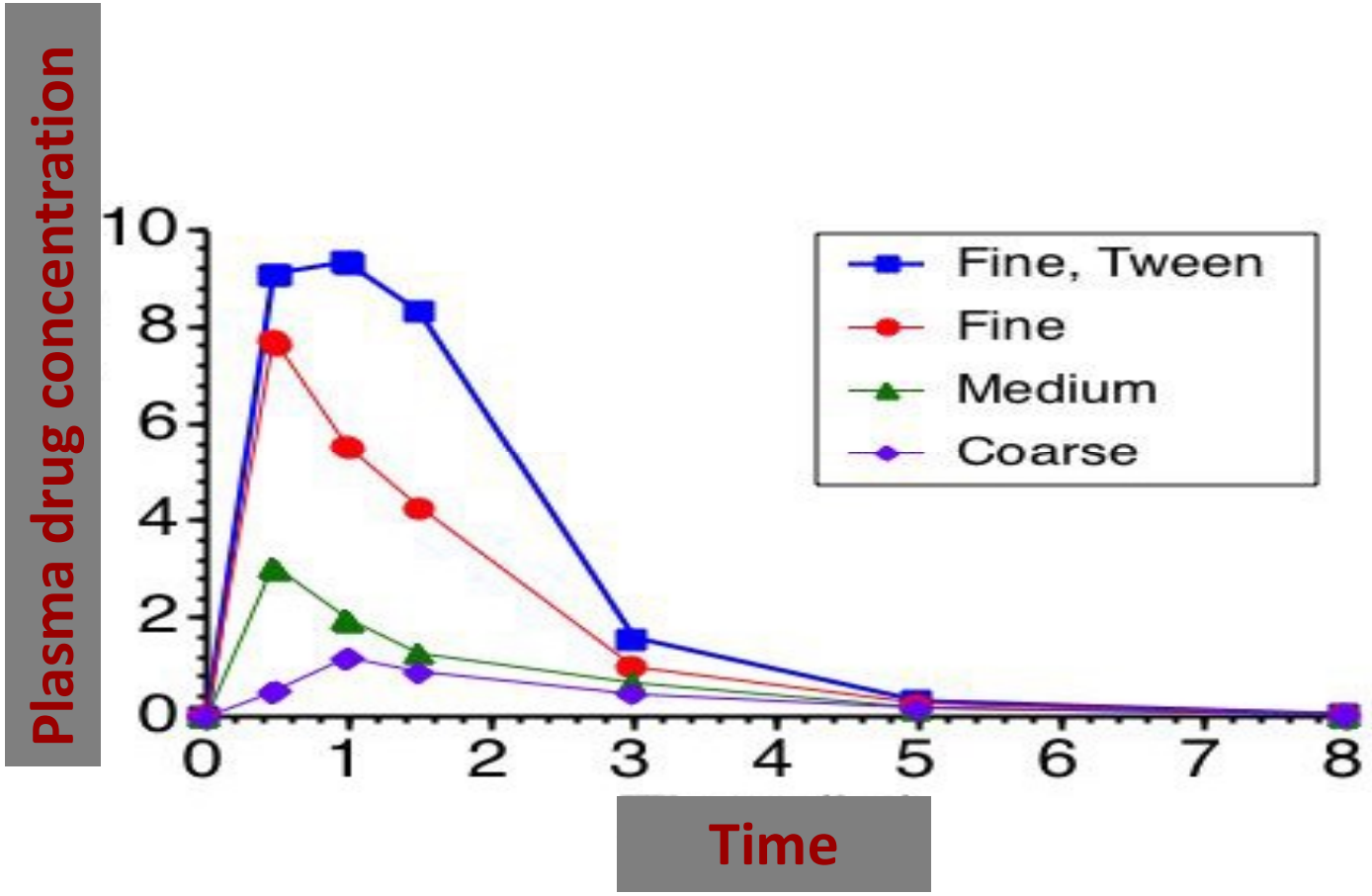
Example

Dose of *griseofulvin* is reduced to one half while dose of *spironolactone* is reduced to one twentieth following micronization

- Disintegrant and SAA increase absorption of poorly soluble drugs

Example. Tween 80 increased BA of Phenacetin

Absorption *versus Particle Size*



NB: Lesser particle size is not always helpful. **Why?**

Reasons

1. Hydrophobic micronized drugs absorb air on their surface, thus decreasing their wettability
2. Particles having size < o.1μm reaggregate to form larger ones
3. Micronization impart surface electrical charge on particles that prevents contact with wetting medium
4. Micronized drugs *are* unstable and degrade quickly in solution. Example: Penicillin-G & Erythromycin
5. Micronization increase gastric irritation

Example: Nitrofurantoin & piroxicam. **So what to be done ?**

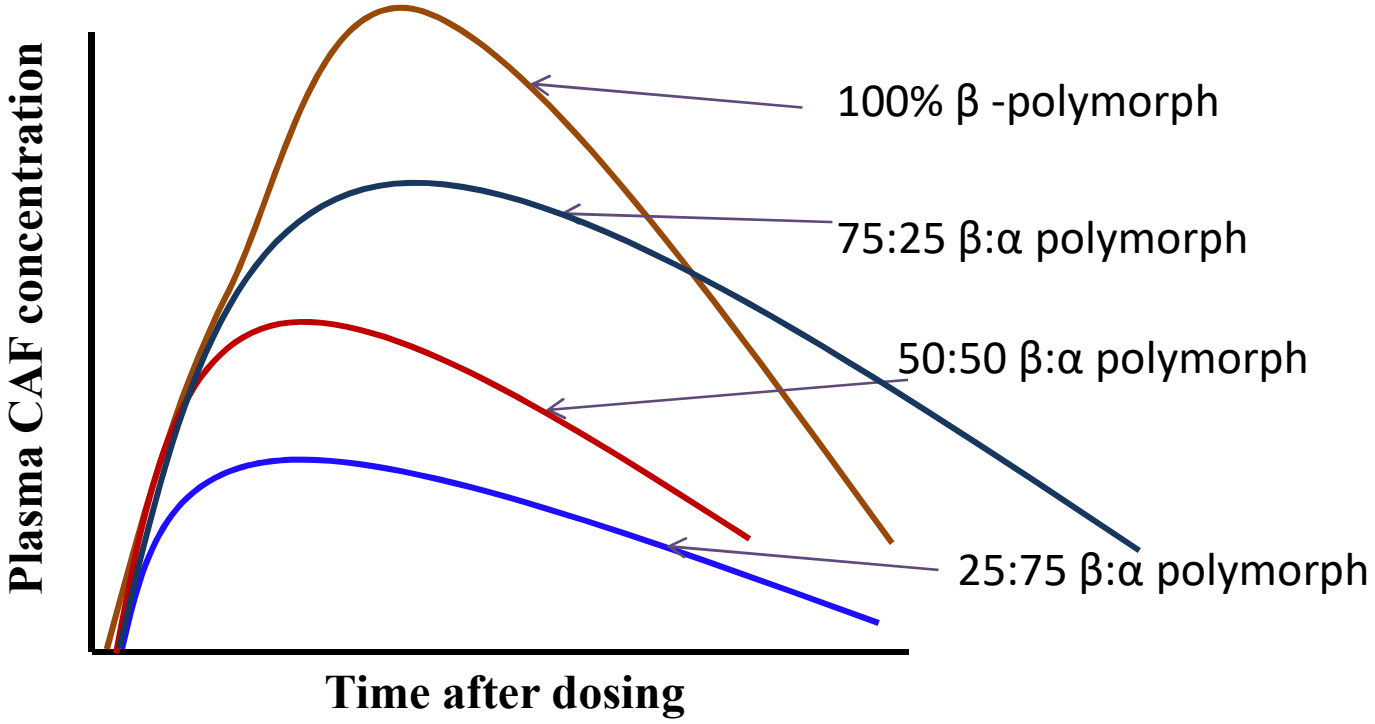
Remedy: Can be overcome by Microencapsulation

B. Crystal Form

- Forms of substance : Crystalline or amorphous
- Polymorphism: Existence of substance in more than one crystalline form [Polymorphs].
- Polymorphs have same chemical structure but d/t physical properties such as solubility, density, hardness, dissolution rate, phase diagrams, hygroscopicity, stability, and rates of reactions, etc.

For instance CAF has several crystal forms: α , β ,ɤ

- When given orally as a suspension, CAF conc. in the body was found to be dependent on the percentage of β - polymorph in the suspension, as it is more soluble and better absorbed. **Why?**



Comparison of mean blood serum levels after the administration of CAF-palmitate suspensions using varying ratios of the stable (α) & metastable (β)

Note

- One of the several forms of polymorphic forms is more stable than the other.
- The stable form has lowest free energy state and high melting point and hence least aqueous solubility
- The remaining polymorphs are called metastable forms which have high free energy state, low mp. and high aqueous solubility
- Amorphous form of drugs have greater aqueous solubility than crystalline form, since the former lacked internal crystal structure but have higher energy states than the latter

C. Solvates & Hydrates

- Many drugs associate with solvent to form solvates

Drug + solvent = crystal = Solvate

- If solvent is water ,then the crystal is called *hydrate*

Drug + H_2O of crystallization = crystal=hydrate

Examples

❖Erythromycin dehydrate dissolves faster than the monohydrate :

Less hydrated → faster dissolution

❖ Ampicillin anhydrous would have faster dissolution than trihydrate but it is less absorbed

Note: Solvate form of drugs with organic solvent may dissolve fast in water than non solvated form.

Why ?

- In general, **crystalline form** of drugs are more rigid and thermodynamically more stable than the amorphous form.
- The crystal form with the lowest free energy is the most stable polymorph.
- A change in crystal form may cause problems in manufacturing the product :
  - ✓incompressibility of granules to tablets
  - ✓cracking in a tablet manufacturing

D. Complexation

- Can influence effective drug concentration in gastrointestinal fluids
- May alter rate and extent of absorption
- Complexing agents can be:
    1. substance normal to GIT such as mucin forms complex with the drug such as Dihydrostreptomycin & Streptomycin
    2. dietary components such as milk forms insoluble complex with TTC

3. Components of a dosage form such as:

- ✓ CaHPO4 as a filler in TTC formulation reduce BA of TTC
- ✓ PEG-4000 in Phenobarbital formulation forms insoluble complex with Phenobarbital

❖ Poor water soluble drugs can be administered as water soluble complexes to enhance BA

Note:

Effect of complexation on drug absorption can be positive or negative depending on whether resulting complex is reversible or irreversible complex

E. Adsorption

- Physical & surface phenomena where drug molecules[Adsorbate] are held on the surface of some inert substances[Adsorbent] by ***vander-wall's forces***

Example:

- ❖ Cholestyramine ↓es rate of absorption of warfarin
- ❖ Charcoal (an antidote) ↓es rate of absorption of promazine
- ❖ Talc↓es rate of absorption of cyanocobolamin.
- ❖ kaopectate ↓es rate of absorption of lincomycin

F. Drug Stability and Hydrolysis In GIT

- Drugs undergo various reactions due to wide spectrum of pH and enzymatic activity of GI fluid namely acid and/or enzymatic hydrolysis

eg. $T_{½}$ of Penicillin G= 1 min. at pH = 1

$T_{½}$ of Penicillin G= 9 min. at pH =2

- So it means Penicillin G is stable at less acidic pH
- Erythromycin and its esters are unstable at gastric fluid ($T_{½}$ Less than 2 min.)

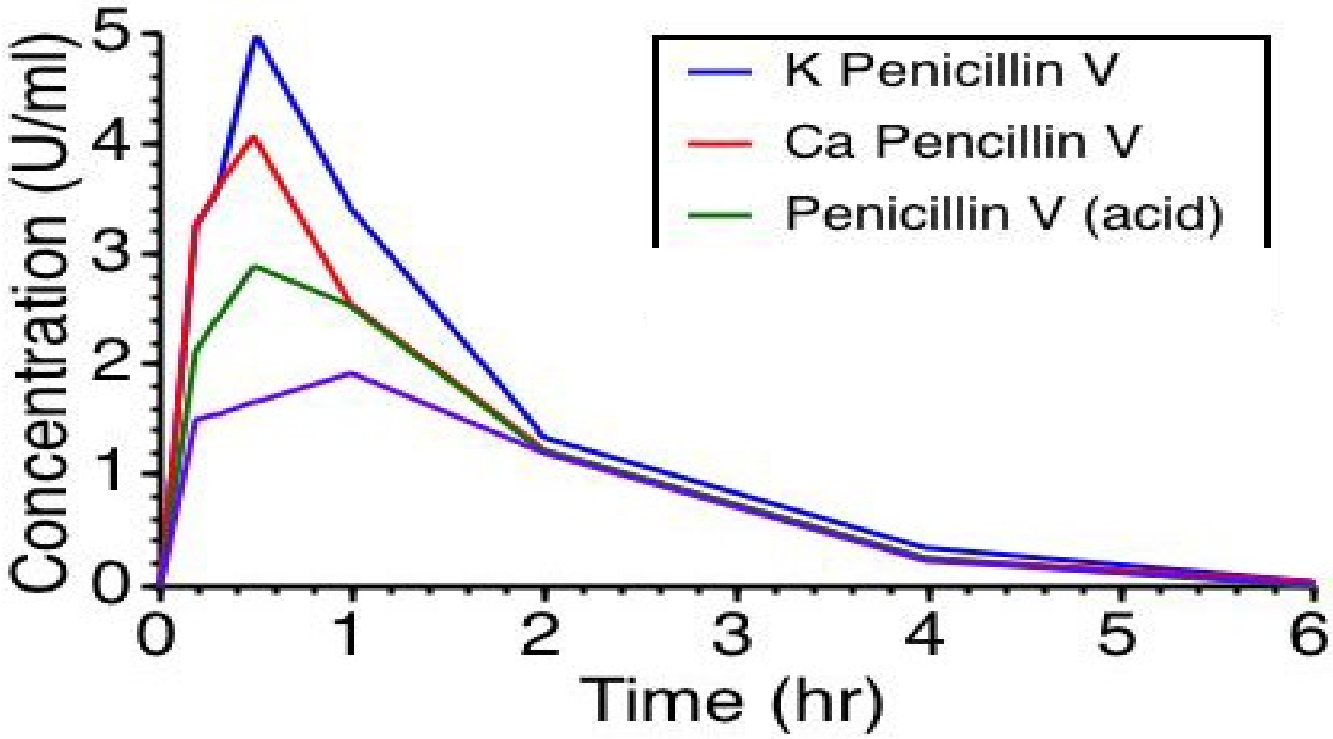
G. Salts

- Na or K salts of weak acid dissolves rapidly than free acid.

Example:. Na salts of Novobiocin shows improved bioavailability

- Certain salts also may have low solubility and dissolution rate.

Example: Al salts of weak acid and pamoate salt of weak base

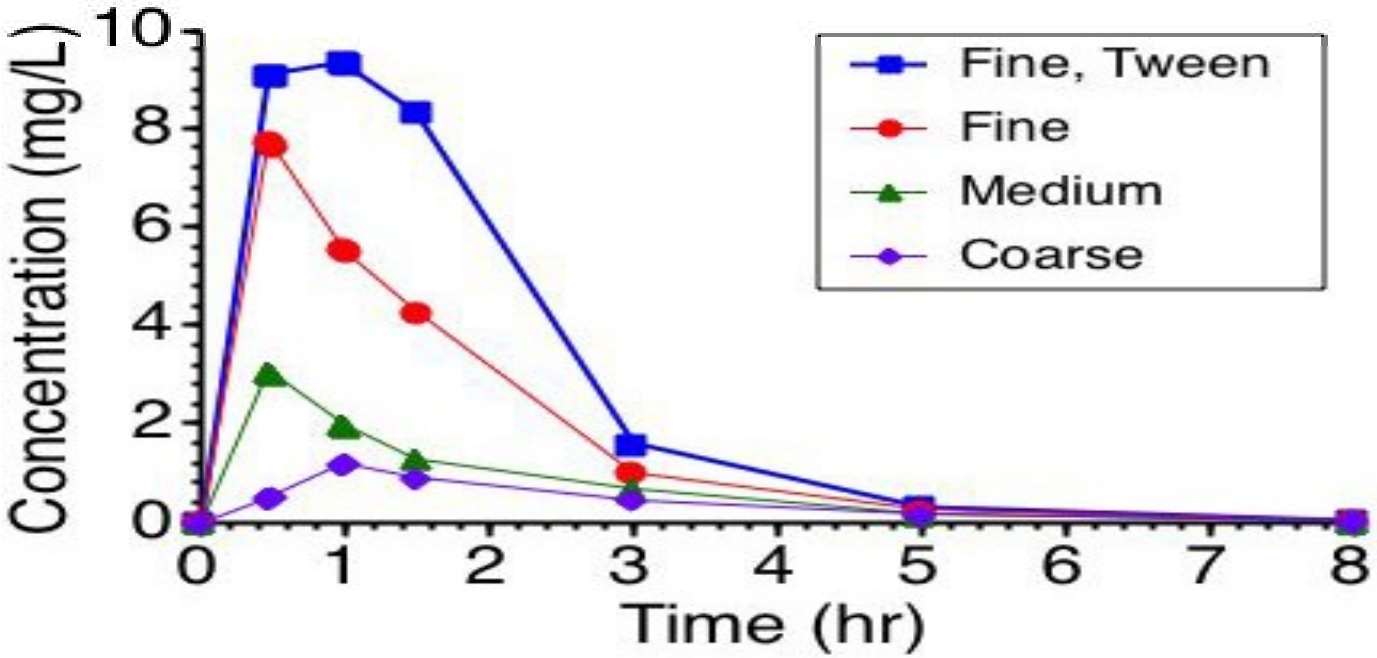


Absorption of penicillin & its different salt forms

H. Presence of Surfactant

- Use of wetting agent and solubilizing agent improve the dissolution rate & absorption of drugs.

Example: Tween 80 increase the rate & extent of absorption of Phenacetin



Dissolution rate

- Dissolution is the process by which a drug becomes dissolved in a solvent.
- For a drug to be absorbed it must first be dissolved in the fluid at the site of absorption.
- The rate at which drugs with poor aqueous solubility dissolve in the GI tract controls the rate of systemic absorption of the drug.

Drugs dissolution can be described by **Noyes-Whitney** equation:

$$\frac{dc}{dt} = DA \frac{C_s - C}{h}$$

- **dC/dt** is the rate of dissolution of the drug particles,
- **D** is the diffusion coefficient of the drug
- **A** is the effective surface area of the drug particles in contact with the gastrointestinal fluids
- **h** is thickness of diffusion layer around each drug particle
- $\mathbf{C_s}$ is saturation solubility of the drug in solution in the diffusion layer and **C** is the concentration of the drug in the gastrointestinal fluids.

Factors affecting dissolution rate

Can be derived from consideration of the terms of the Noyes-Whitney equation and knowledge of the factors that in turn affect these terms

1. Surface area

- The smaller the particle size, the greater the effective surface area exhibited by a given mass of drug, and the higher the dissolution rate.
- Increase bioavailability of dissolution-rate limited drug

Example: Griseofulvin

10 μm (SA= 0.4 $m^2 g^{-1}$) ⟶ 2.7μm (SA= 1.5 $m^2 g^{-1}$)

- Double the amount of drug absorbed

2. Solubility in the diffusion layer, C_s

- C_s is saturation concentration of drug in the diffusion layer
- approximated by the maximum solubility of the drug in the solvent
- Affects the concentration gradient ($c_s - c_t$)
- Level of C_s is pH dependent:
  - Solubility of weak acids increases with increasing pH
  - Solubility of weak bases decreases with increasing pH

3. Salt form

- Dissolution rate of a salt form of a drug is generally quite different from that of the parent compound
- Salt form of a drug is more soluble in an aqueous medium
- Increase dissolution rate
- Improved bioavailability

4. Drug form: Crystal or Amorphous

Solid drug materials may occur as pure crystalline form, polymorphic form, or solvate form:

- Pure crystalline substances having definite shape
- Amorphous particles are without definite shape
  - Amorphous form usually dissolves more rapidly than crystalline form(s)
  - Significant differences in bioavailability exists b/n amorphous and crystalline forms of drugs

➢Polymorphic form

- ✓Solid **crystalline phase** of a given compound resulting from the possibility of different arrangements of that compound in the solid state exist as stable, metastable.
- ✓ A metastable polymorph usually exhibits a greater dissolution rate than the corresponding stable polymorph.

Example: Chloramphenicol palmitate

- The extent of absorption of Chloramphenicol increases as the proportion of the ß-polymorphic form of Chloramphenicol palmitate is increased.

Solvates

- Solvated and non-solvated forms usually exhibit differences in dissolution rates.
  - ➢ Differences in bioavailability
- Greater solvation of crystal means lower solubility and dissolution rate in solvent identical to solvation molecule

J) pH partition theory (Brodie) :

- Explains drug absorption from GIT & its distribution across biomembrane
- Most drugs are either weak acids or weak bases;thus their degree of ionization depends upon pH of biological fluid
- Drugs that are transported by passive diffusion depend upon:
    - ❖ dissociation constant:pKa of the drug
    - ❖ lipid solubility, o/w partition coefficient ,pH at absorption site

- For a drug to be absorbed, it should be unionized since unionized proportion is lipid soluble
- Fraction of drug remaining unionized is a function of both pKa and pH of solution

The assumptions of pH partition theory :

1. GIT acts as a lipoidal barrier to the transport of drug
2. Rate of absorption of drug is directly proportional to its fraction of unionized drug
3. The higher the lipophilicity of unionized portion, the better the absorption.

4. Rate of absorption of a drug is related to o/w partition coefficient of a drug:

- The more lipophilic the compound, the faster is the absorption

5. Acidic & neutral drugs are absorbed from stomach but basic drugs are not
6. Basic drugs are absorbed better from small intestine but acidic drugs are not.

Note: There is deviation from assumptions of pH partition theory

- Most weak acid drugs are well absorbed from small intestine than from stomach due to large surface area & a relatively long residence time in SI.

- The primary limitation of pH partition theory is due to the assumption that only unionized drugs are absorbed while in fact ionized drugs are also absorbed, albeit at a slower rate

K.Drug solubility

- The absorption of drug requires that molecule be in solution at absorption site.
- Dissolution, an important step, depends upon solubility of drug substance.

pH solubility profile:

- pH environment of GIT varies from Acidic in stomach to slightly Alkaline in a small intestine.

Types of Drugs	soluble in
– Basic drugs	Acidic medium(stomach)
– Acidic drugs	Basic medium(intestine)

Improvement of solubility:

- Addition of acidic or basic excipient
- Example: Solubility of Aspirin (weak acid) increased by addition of basic excipients.
- For formulation of controlled release dosage , buffering agents may be added to slow or modify the release rate of a fast dissolving drug.

i. Write true or false & give reason for each answer

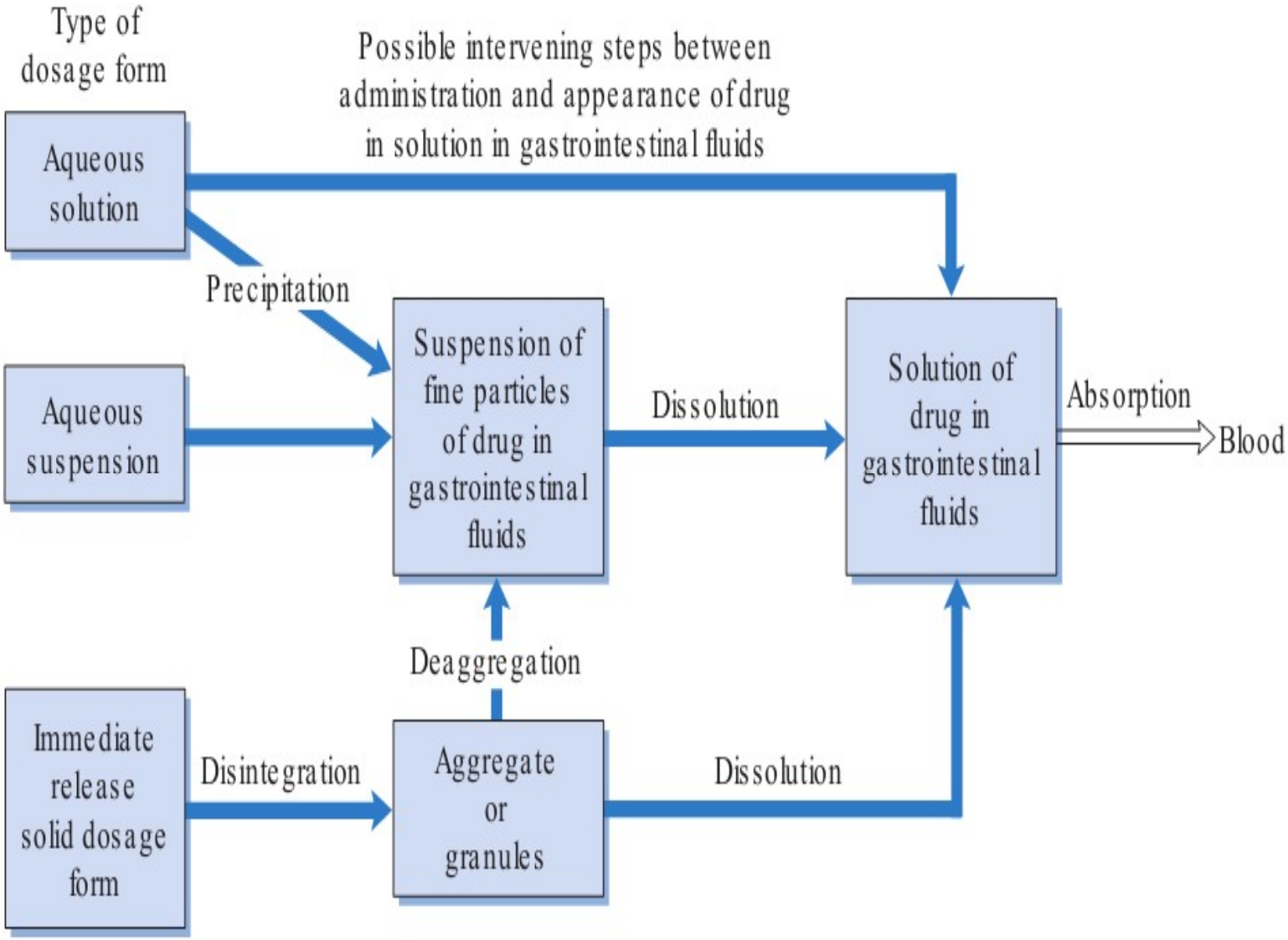
1. **Bioavailability of predinisolone is higher if taken after meal**
2. **Unstirred water layer has no impact on drug absorption rate, particularly if the drug is absorbed by passive diffusion**
3. **Diffusion coefficient is an inherent property of a drug**

ii. Answer the following question based on the given information

Equal dose of drug-x is administered into the portal vessel And via oral rout. The bioavailability of drug-x given via portal vessel is higher than its orally administered bioavailability but less than IV given equal dose. Explain.

2.3. Formulation factors affecting oral drug absorption

- Bioavailability of a drug can be influenced by factors associated with the **formulation** of the dosage form
- The type of dosage form influence the number of possible intervening steps **between administration and the appearance of dissolved drug** in the GI fluids.
- The greater the number of intervening steps, the greater will be the number of potential obstacles to absorption.


Type of dosage form
Possible intervening steps between administration and appearance of drug in solution in gastrointestinal fluids
Aqueous solution
Precipitation
Aqueous suspension
Suspension of fine particles of drug in gastrointestinal fluids
Dissolution
Solution of drug in gastrointestinal fluids
Absorption
Blood
Deaggregation
Immediate release solid dosage form
Disintegration
Aggregate or granules
Dissolution

- Absorption rate of orally administered drug depends on:
    i. Dosage form administered
    ii. Ingredients used to manufacture drug products
    iii. Methods/procedures used to make dosage forms

i. Dosage form administered

- Relative order of bioavailability of drug from different dosage forms is presented as following :
- Solutions > Suspensions > Emulsion > Capsules > Compressed Tablets > Coated tablets

A. Solutions

- Formulation as a solution normally eliminates the in vivo dissolution step and presents the drug in the most readily available form for absorption.
- Thus solutions have maximum bioavailability as compared to others
- Absorption from oral solution is rapid and complete
  - ➢ The rate limiting step is often the rate of gastric emptying.

Note:

Some drugs which are poorly soluble in water may be dissolved in cosolvent [i.e., mixed water/alcohol or water/glycerol solvents] to form solution

Factors affecting absorption from solution:

1. Chemical stability of drug in solvent & gastrointestinal fluid
2. Complexation between drug & excipients just to ↑ solubility, stability of drug
3. Viscosity: viscous versus less viscous solution
4. Types of solution: aqueous or oily solution

Which one has higher rate of absorption ? Why?

5. Solubilization: Incorporation of drug into solubilizing agent to enhance its solubility

Approaches:

- **Cosolvent approach**
  - Useful for drugs having:
    - tight crystal structure
    - higher melting points
    - relatively less ionic properties, **Why?**
  - Crystal structure that is broken by Cosolvent
- **Complexation approach:** Drug-CD complex
- **Micellization approach**

B. Suspension

- Comes next to solution with respect to BA
- A useful dosage form for administering insoluble or poorly water-soluble drugs.
- Usually, absorption of a drug fro suspension is dissolution-rate limited.
- However, a suspension of a finely divided powder in the presence of SAAs will maximize the potential for rapid dissolution.
- Hence, dissolution of all drug particles commences immediately on dilution of suspension in the gastrointestinal fluids

Factors affecting absorption of drug from suspensions

1.Particle size of dispersed phase

2.Effective surface area of dispersed phase

3.Crystal form of drug: some drugs can change their crystal structure.

Example. i. Sulfathiazole changes its polymorphic form, which can be overcome by adding PVP.

ii. α, -CAF has less serm conc. than ß-CAF and γ-CAF

iii. Oxytetracycline-A & Oxytetracycline-B [metastable form]

4. Complexation: Formation of non-absorbable complex between drug and other ingredients.
5. Inclusion of surfactant

   Eg. Absorption of phenacitin from suspension is increased in presence of tween 80.
6. Viscosity of suspension

   Eg. Methyl cellulose reduces the rate and extent of absorption of nitrofurantoin by increasing its viscosity

C. Capsules

- The gelatin shell should disrupt rapidly and allow the contents to be mixed with the GI tract contents.
- The capsule contents are subjected to relatively low compression forces that might not reduce effective surface area, thus enabling capsule performance better than a tablet. This is not always the case!
- For hydrophobic drug dispersing agent should be added to the capsule formulation.

Reason: to ↑powder dispersion by minimizing aggregation &maximizing its surface area.

- Two types of empty gelatin capsule

  a_1. Hard gelatin capsule

  a_2 . Soft gelatin capsule

a_1. Hard gelatin capsule [HGC]

Factors affecting rate of drugs absorption from HGC :

- Dissolution rate of gelatin shell
- Rate of penetration of GI fluids into encapsulated mass : Hydrophilic vs lipophilic mass?
- Rate at which mass disaggregates in the GI fluid
- Rate of dissolution of disaggregated mass
- Effect of excipients[diluents, lubricants ,wetting characteristics of drug, packing density , etc]

a_2. Soft gelatin capsule [SGS]

- Has a gelatin shell thicker than HGS,but shell is more plasticized by adding glycerin,sorbitol
- Used to fill non aqueous solution or liquid or semi solid.

Why not aqueous?

- Drugs from SGC has better BA than from HGC
- Filled SGC has BA equivalent to emulsions. Why??

Example:

- ✓ Quinine base was better absorbed from SGC compared with its HCl salt from HGC .
- ✓ Grieseoflavin exhibited 88% absorption from SGC compared to its absorption from HGC(30%)

D. Tablets

- The most commonly used oral dosage form.
- Quite complex in nature. Why?
- The biggest problem is overcoming the reduction in effective surface area produced during compression process.
- These processes necessitate the addition of excipients, which serve to return the surface area of the drug back to its original precompressed state

Formulation components & conditions affecting bioavailability

- Physicochemical properties of the liberated drug particles in the gastrointestinal fluids, e.g. wettability, effective surface area, crystal form, chemical stability
- Nature and quantity of diluent, binder, disintegrant, lubricant and any wetting agent
- Type of the tablet (uncoated, coated, enteric-coated)
- Drug-excipient interactions (e.g. complexation)
- Compaction pressure and speed of compression used in tabletting
- Storage conditions and age of the tablet

Effect of excipients

- Drugs are almost never administered alone but as DFs

  Drug(s) + Excipients → Manufacturing process → Dosage form

- Excipients are added to ensure acceptability, physico-chemical stability during the shelf life, uniformity of composition and dosage, manufacturability and optimum bioavailability
- Facilitate tablet processing or release of drug from tablets as they influence rate and/or extent of absorption

1. Diluents(fillers)

- Hydrophilic diluents (e.g. Lactose, microcrytalline cellulose)
  - Promote dissolution of poorly water soluble hydrophobic drugs (such as spironolactone) by forming a coat on hydrophobic drug particles and rendering them hydrophilic
- Drug-diluent interaction may result in poor drug bioavailability

E.g. Poorly soluble, unabsorbable complex is formed between:

- Tetracyclines and dicalcium phosphate
- Amphetamine and sodium CMC
- Phenobarbitone and PEG 4000

- Epileptic patients who stabilized with sodium phenytoin capsules containing calcium sulphate dihydrate as diluent, developed clinical features of phenytoin over-dosage when given sodium phenytoin capsules containing lactose at identical dose (400 mg daily dose).

Reasons:

- Calcium sulphate dihydrate was responsible for decreasing phenytoin gastrointestinal absorption
  - Forms poorly absorbable ***calcium-phenytoin complex*** *thereby d*ecreasing its GI absorption
- Lactose increased bioavailability of phenytoin for same dose as it never form nonabsorbable complex with phenytoin
  - Higher plasma levels exceeded max. safe conc.
    - ✓ Produced toxic side-effects

2. Disintegrants

- Required to break up capsules, tablets and granules into primary powder particles thereby increasing SA
- Amount & type of disintegrants is crucial
  - Decrease in disintegrant amount can significantly lower BA by prolonging disintegration time
  - Disintegrants with high swelling or hydration capacity exhibit high tablet/capsule disintegration rate and rapid drug dissolution rate
  - Superdisintegrants such as crosscarmellose, crospovidone, sodium starch glycolate increase rate and extent of dissolution, and improve drug bioavailability

3. Binders

- Concentration and chemical nature of the binder may interfere or retard tablet disintegration & slow dissolution rate of drug
  - Increasing binder conc. increases tablet cohesiveness, hardness & hence retards its disintegration.
  - Certain binders such as methyl hydroxy ethyl cellulose form a coat around drug particles retarding their dissolution
- Hydrophilic binders such as starch, gelatin, PVP imparts hydrophilic properties to granule surface there by triggering better dissolution of poorly wettable drug.

4. Lubricants

- Commonly included during tablet compression and capsule filling operations to reduce friction b/n powder and metal surfaces during manufacture.
- Some hydrophobic lubricants such as Magnesium stearate retards wettability and liquid penetration into capsule and tablet there by decreasing drug dissolution rate & BA

How to overcome lubricant induced slow drug release rate?

- Addition of wetting agent (i.e. water-soluble surfactant) and use of hydrophilic diluents
- Use of soluble lubricants such as sodium stearyl fumarate,

5. Surfactants

- Used in DFs as emulsifying , wetting, solubilizing agents or suspension stabilizers
- Capable of either increasing or decreasing bioavailability by interacting with either the drug, the membrane or both
- **Surfactants can increase absorption of drugs by:**
  - Promoting wetting e.g. Tween 80 with phenacetin
  - Enhancing membrane permeability.
    - ✓Surfactant monomers potentially disrupt integrity and function of biological membrane, thereby enhancing drug penetration across GI barrier.
- **Surfactants can decrease absorption of drugs by:**
  - Formation of unabsorbable drug-micelle complex at surfactant concentration above CMC
  - Laxative action induced by large surfactant concentration

6. Coating layers

- Coating adds another barrier between solid drug and GI fluid
- **Sugar coating :** Sealing by shellac, and thickness of the coat delay dissolution
- **Non-enteric film coating, :** soluble, dispersible in GI fluid
  - HPMC, povidone, PEG can be used for such purpose
- **Enteric film coating, :** resistant to gastric fluid, soluble at Ph ≥5
  - Cellulose acetate phthalate, eudragit (acrylate polymer)
- In general, the deleterious effect of coating materials on drug dissolution from tablets is in the order of:

enteric coat > sugar coat > non-enteric film coat

7. Viscosity-enhancing agents

- Employed in liquid DFs for oral use to control palatability, pourability and rate of sedimentation of dispersed particles
- Often hydrophilic polymer(e.g. acacia, tragacanth,) or semi synthetic gums (eg. Carboxymethylcellulose(CMC), MC)
- May produce change in GI absorption of drug, by:
  - **Complex formation b/n drug and hydrophilic polymer**
    - ✓Reduce drug in solution available for absorption

      E.g. Sodium CMC forms complex with amphetamine
  - **Increase viscosity**
    - ✓Act as mechanical barrier to the diffusion of drug from dosage form into the bulk of GI fluid and from GI fluid to mucosal lining.

8. Vehicles or solvent systems

A. Aqueous (e.g. Water, syrup)

B. Non aqueous water miscible (e.g. Propylene glycol, glycerol, sorbitol)

- Aqueous & non aqueous water miscible vehicle are miscible with GI fluid
- Drugs from these vehicles are rapidly absorbed

C. Non aqueous water immiscible (vegetable oils)

- Release from water immiscible vehicles depend on drug partition from the oil phase into the aqueous GI fluid

Coating tablet

- ✓ Protection [From what?]
- ✓ uneven coating can cause non-uniform release of active ingredient

  Example:

  i. Enteric coatings : Designed to permit safe passage of tablet via the acid environment of the stomach to the more suitable juices of the intestines [coating polymer is usually cellulose acetate phthalate, CAP.]. Why CAP ?

ii. Film-coatings :employed to protect drug substance from destructive influences of moisture, light and air throughout their period of storage or to conceal a bad or bitter taste from the taste buds of the patient. [Coating agent: HPMC]

iii. Sugar-coatings

- Conceal bitter taste (liquid glucose, sucrose)
- Protect drug from moisture during its shelf-life
- Coating polymer can be Shellac

Drawback of shellac:

Think of its aging problem due to repolymerization

Unit 3. Principles of Bioavailability of Drugs

3.1. Background: What is Bioavailability?

3.2. Factors Affecting Bioavailability (summary)

3.3. Absolute and Relative Bioavailability

3.4. Methods of Assessing Bioavailability

3.4.1. In Vivo Approaches

3.4.2. In Vitro Approaches

3.4.3. Dissolution

3.5. In Vitro in Vivo Correlations

3.6. Bioequivalence

3.1. Background : **What is bioavailability?**

- "The rate and extent to which active ingredient or active moiety is absorbed from a drug product and becomes available **at the site of action**."[U.S. FDA]

- It is a pharmacokinetic term that refers to rate and extent to which a drug reaches **its site of action** or a **biological fluid** such as blood that has access to its site of action

Is it practical from site of action??

- **However, practical determination of concentration of drug at the site of action such as receptor site is rare since** it cannot be readily measured directly at the site of action.
- However , most BA studies involve determination of drug concentration in blood or urine.
- Thus, BA study is an indirect measure of drug response by monitoring drug levels in the blood or urine

Assumption:

Drug at site of action ⟷ **Drug in blood**

- Thus, bioavailability is more commonly defined as "the rate & extent of drug absorption from a dosage form & extravasscular absorption site & available in the **systemic circulation"**
- It is concerned with how quickly and how much of a drug appears in the blood after a specific dose is administered

Note:

Systemic circulation from BA point of view refers to venous blood plasma but not blood plasma in arteries and/or hepatic portal vessel . **Why?**

Bioavailability of drugs used for acute case

- Rapid & complete absorption is usually desirable for drugs used on acute or as needed basis for pain, allergic response, insomnia. **Why?**
- The more rapid the absorption, the shorter is the onset & the greater is the intensity of pharmacological response
- The efficacy of a single dose of a drug is a function of both the rate & extent of drug absorption

3.2. Factors affecting bioavailability of a drug [Summary]

1. Factors related to components of a formulation & manufacturing variables

- Properties of the drug (salt form, crystalline structure, formation of solvates, and solubility).
- Composition of the finished dosage form (presence or absence of excipients and special coatings).
- Manufacturing variables (compression force, processing variables and environmental conditions).
- Rate and/or site of dissolution in the git

2. Physiologic factors affecting bioavailability

- Contents of the git (fluid volume and pH, diet, ± of food, bacterial activity, and presence of other drugs)
- Rate of git. transit (influenced by disease, physical activity, drugs, emotional status, and composition of git contents).
- Presystemic drug metabolism and/or degradation (influenced by local blood flow; condition of git membranes; & drug transport, metabolism, or degradation in git. or during hepatic first pass)
- Age, sex, race, disease, body size, time of day, and physical activity.

3. Other factors affecting bioavailability

- Physiologic & pharmacokinetic perturbation that affect concentration of drug measured in fluid samples can potentially influence results & interpretation of BA study.

Example:

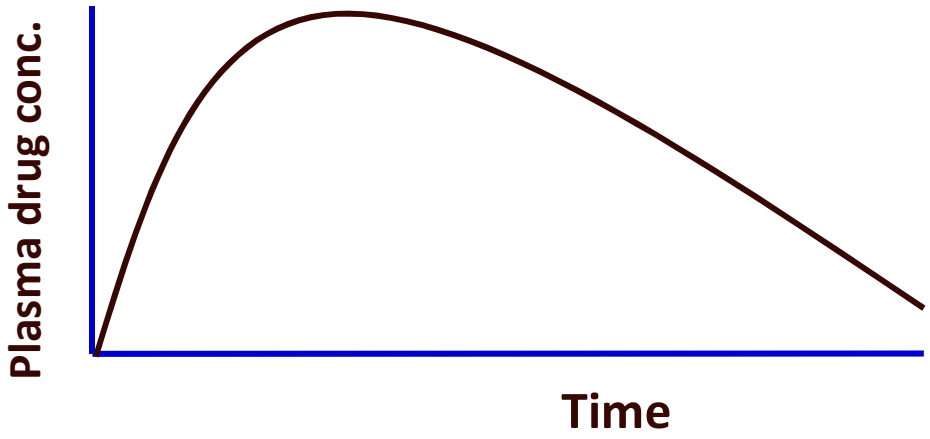
- Rate, extent &/or route of metabolism (e.g., coadministered drugs that compete for or induce drug metabolizing enzymes)
- Rate &/ or extent of drug elimination by kidney (e.g., kidney disease &/or competition & changes in urine pH that affect renal transport mechanisms
- Degree of binding of drug to plasma or tissue proteins (e.g., age-related changes in plasma-binding proteins or protein-binding displacements
- Distribution of drug into the erythrocytes

3.3. Types of bioavailability

- **Absolute bioavailability**
- **Relative bioavailability**

Note:

The **A**rea **U**nder the drug **C**oncentration - time curve [AUC] is used as a measure of the total amount of an altered drug that reach the systemic circulation



Area under plasma drug concentration- time curve [AUC]

Absolute bioavailability[ABA]:

- ABA is systemic availability of drug after extravasscular administration .
- The fraction[F] of an administered dose which actually reaches the systemic circulation ranges from F = 0 (no drug absorption) to F = 1 (complete drug absorption). Thus, F = ABA
- Knowledge of F is needed to determine appropriate oral dose of a drug relative to IV dose.
- For drugs given Iv, F= 1 or 100% while for all extravascularly given drugs , F≤1.

- Total amount of drug reaching systemic circulation is directly proportional to area under the plasma drug concentration as a function of time curve (AUC)
- ABA is thus determined by comparing the respective AUCs of the test product after extravasscular & intravenous administration.
- Intravenous route is the **reference standard** since the dose is, by definition, completely available.

$$\mathbf{F = AUC_{ev} / AUC_{iv}}\text{ , when equal doses are used}$$

(where AUC_{ev} and AUC_{iv} are, respectively, area under plasma concentration-time curve following extravascular & intravenous drug administration)

Note:

Determination of absolute bioavailability involves:

- Intravenous administration of standard product
- Extravascular administration of test product
- Setting ratio of oral to intravenous AUC values normalized for dose if different doses are used ; i.e.,

$$\mathbf{ABA = F = (AUC_{oral} / AUC_{iv}) \times (Dose_{iv} / Dose_{oral})}$$

Relative or Comparative bioavailability [RBA]

- Availability of drug from test product as compared to another dosage form or drug product of the same drug given in the same dose.
- Availability of drug from a drug product as compared to a recognized reference product, usually solution.
- These measurements determine the effects of formulation differences on drug absorption.
- RBA of product A compared to product B, both products containing the same dose of the same drug, is obtained by comparing their respective AUCs.

- RBA of two products given at the same dosage level and same route of administration is obtained from:

$$\mathbf{RBA. = AUC_A / AUC_B}$$

- When different doses are used via same route, correction factors are made as follow:

$$\mathbf{RBA. = [AUC_A / AUC_B] \times [Dose_B / Dose_A]}$$

- **Percent RBA = RBA x 100**

Note: Drug product B is the reference standard while A is the test product.

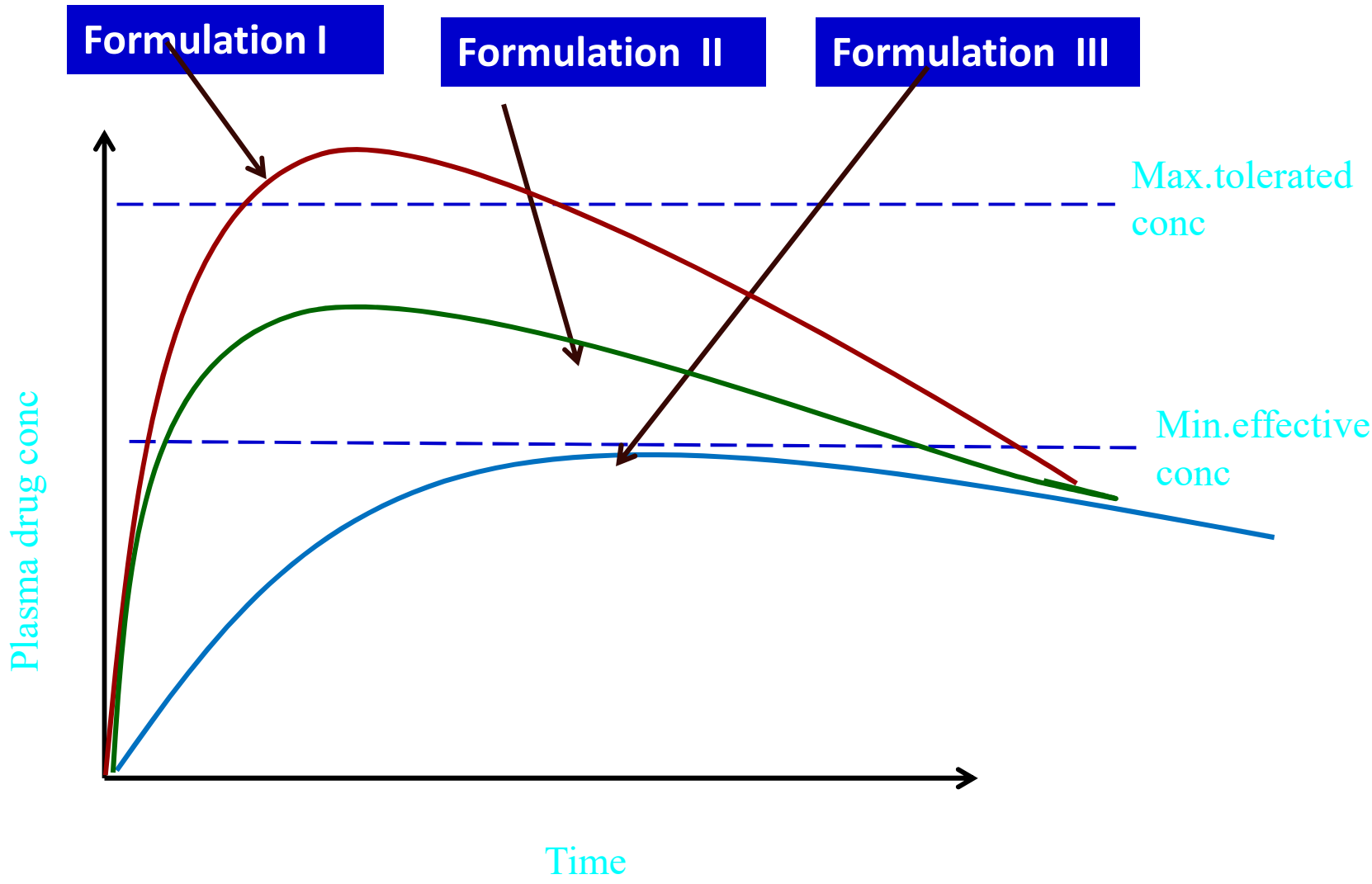


Illustration of Relative BA

Note

Plasma concentration time curves for three formulations with different rate of drug absorption

- Achieved plasma concentrations can be controlled by the rate of drug absorption
- Formulation I would be toxic. A smaller dose, or a slower release formulation should be considered.
- Formulation II appears to be effective in the dose and formulation used.
- Formulation III appears to be too slow and thereby ineffective. If it is a drug requiring a sustained effect this formulation may be more useful at a higher dose or after repeated doses.

Note.

1. Determination of Relative Bioavailability requires:
   - no I.V. reference standard
   - comparison of AUC values (ratio) of different dosage forms / formulations

$$Rel.BA = (AUC_a / AUC_b) * (Dose_b / Dose_a)$$

2. Considering BA of a generic product in relation to brand of same drug implies determining its RBA.
3. A more general form of the equation results from considering the possibility of different doses, as follow:

$$\mathbf{RBA = [AUC_g / Dose_g] \times [Dose_b / AUC_b]}$$

Where ,g=generic formulation , b=Brand formulation

3.4. Methods of assessing bioavailability of drug

Bioavailability testing [study] is a means of :

- ❖predicting the clinical efficacy of a drug
- ❖getting a direct evidence concerning efficiency with which a dosage form performs its intended therapeutic function.
- ❖Comparing availability of a drug substance:
  - ✓from different dosage forms or
  - ✓from the same dosage form produced by different manufacturers.

Types of methods used to assess drug bioavailability

1. In Vivo approaches

- Measurements of plasma drug concentration
- Measurements of amount of drug excreted in urine, unchanged

2. In Vitro approaches

- Drug dissolution

3.4. 1. In Vivo approaches

i. Measurement of blood or plasma drug concentration

- Relatively easy to conduct and requires a limited number of subjects
- Single dose of the drug product is administered to a panel of normal, healthy adult[18 to 35year old).
- Blood samples are collected over a regular period of time following single dose administration
- Collected samples are analyzed for drug content using HPLC
- A profile is constructed showing blood drug concentration at specific times at which the samples were taken
- Based on the blood concentration as a function of time, inferences are drawn regarding bioavailability of drug based on certain key parameters

What key parameters should be measured to determine drug BA ??

The key parameters to be measured are:

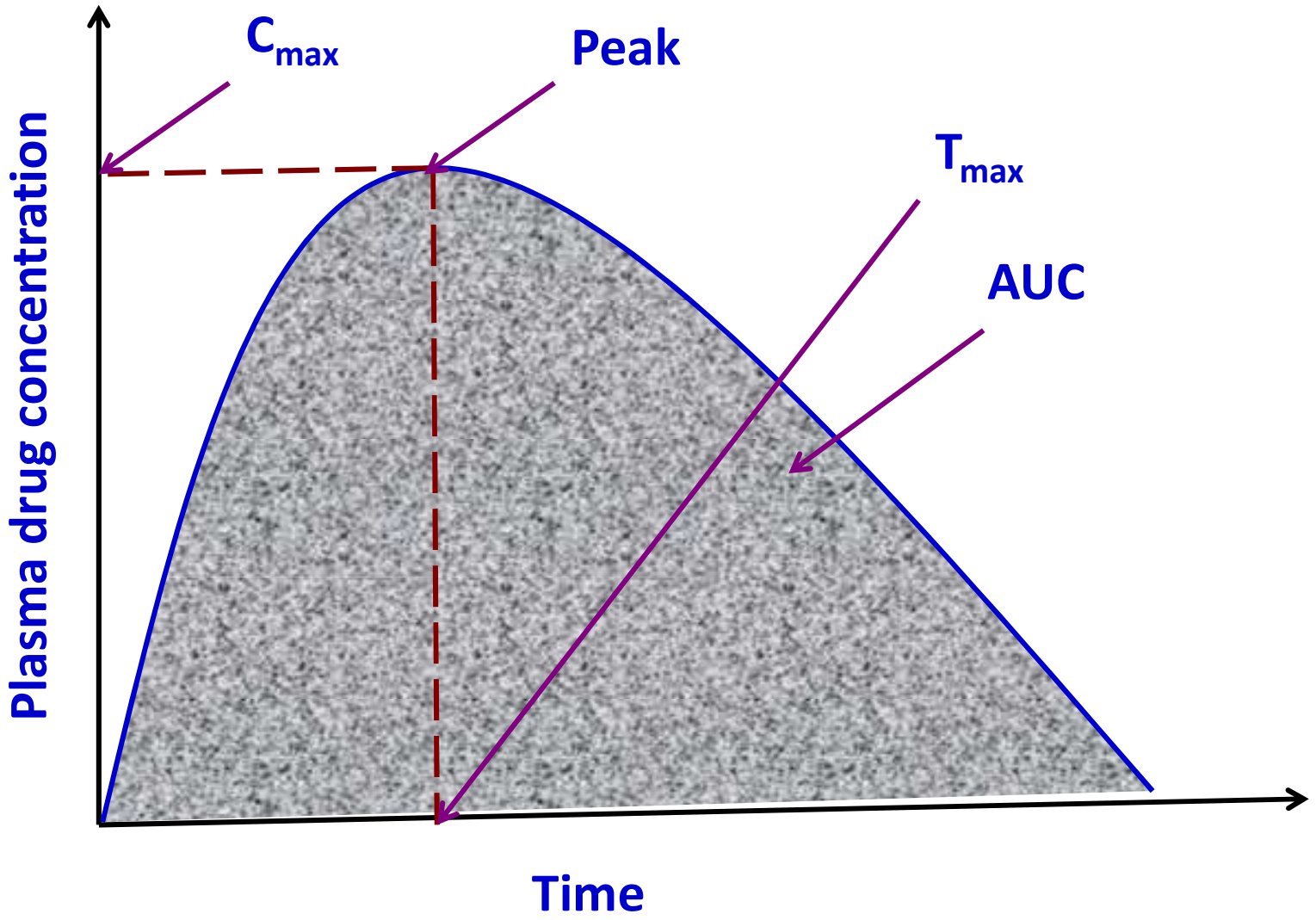
1. **Area under the plasma concentration-time curve, AUC**
   - It is the area from t=o to t=∞
   - Proportional to total amount of drug reaching systemic circulation unchanged
   - Characterizes extent of drug absorption
   - Directly proportional to drug dose
   - Inversely related to rate of drug elimination from the body

2. Maximum [peak] plasma drug concentration, C_{max}.

- Function of both rate & extent of drug absorption
- Increases with an increase in dose & absorption rate

3. T_{max}.

- Time at which the C_{max} occurs
- Reflects rate of drug absorption
- Decreases as absorption rate increases


C_{max}
Peak
T_{max}
AUC
Plasma drug concentration
Time

Note:

1. Extent of systemic availability is determined by extent of drug absorbed from the site of administration, and is influenced by the drug, the dosage form and the interaction of these with the complex environment of the absorption site.
2. For a drug that obeys linear pharmacokinetics, AUC & C_{max} values increase proportionately with dose.
3. If two formulations (dosage forms) of same drug exhibit comparative AUC values, then they are considered to have similar BA
4. Bioavailability of oral dosage form is generally compared with intravenous solution (100% standard), to determine its absolute bioavailability

ii. Urinary Excretion data [indirect measures] of BA

- Used for drugs obeying non-linear kinetics
- Such drugs are characterized by the following features:
  - ✓ Changes in AUC and C_{max} values are not proportional to administered dose.
  - ✓ Plasma-concentration- time profile cannot be used as indicator of absolute bioavailability since either absorption, distribution, metabolism or excretion processes which handle the drug are saturated i.e. their capacity has been exceeded within therapeutic concentration range of the drug substrate.
- Therefore, absolute bioavailability assessment is done by measuring extent of the drug and its metabolites excreted in the urine.

- Measures cumulative amount of unchanged drug excreted in urine.
- Involve collection of urine samples & determination of total quantity of drug excreted in urine as a function of time
- Urinary excretion of unchanged drug is:
  - ✓directly proportional to plasma concentration of total drug.
  - ✓a reflection of quantity of drug absorbed from extravasscular site.

- Used to measure bioavailability of drug from urine

➢ **Percent relative BA= $[(D_u)_A^{\infty} / (D_u)_B^{\infty}]$**

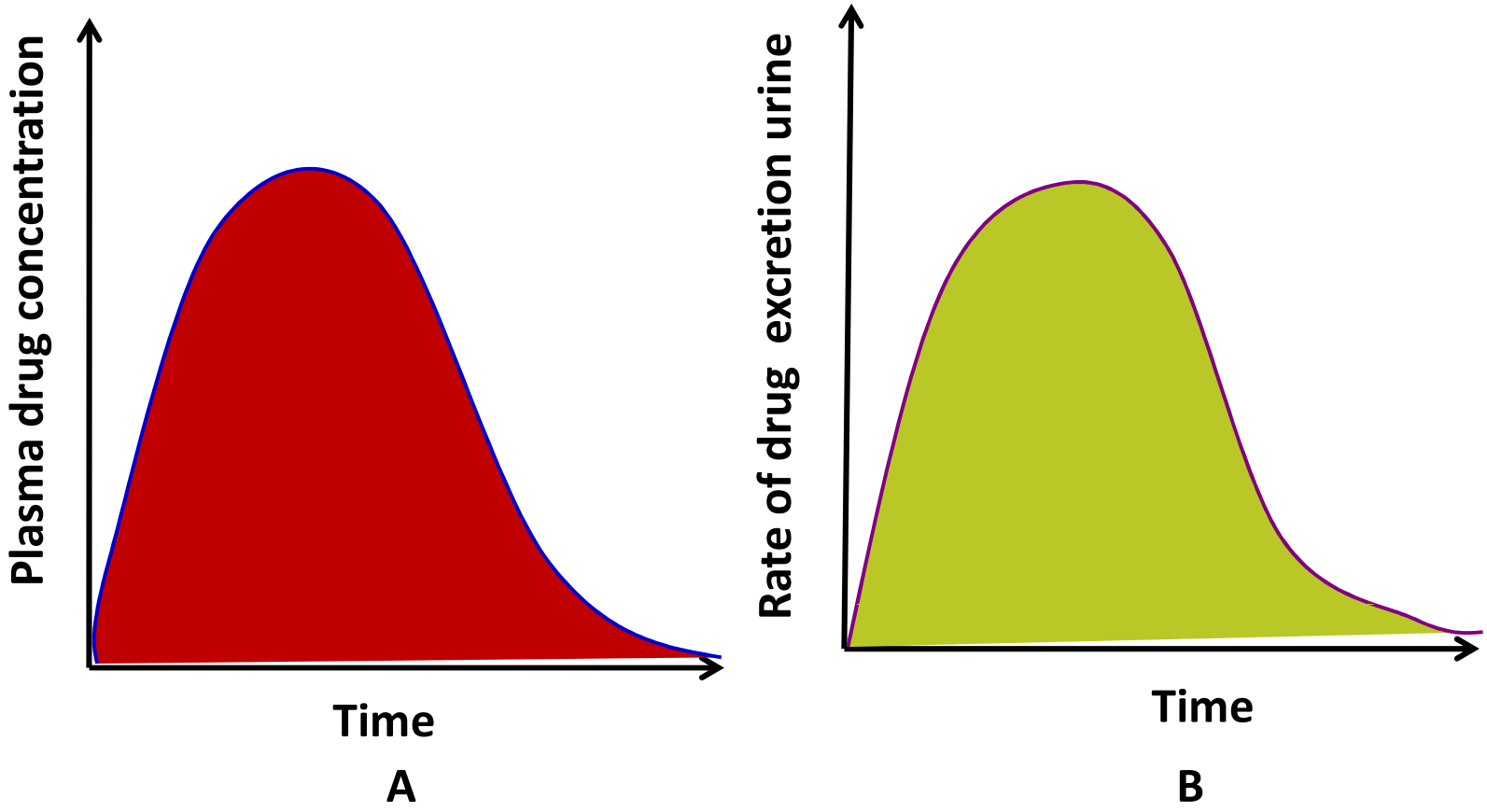
where $(D_u)^{\infty}$ is the total amount of drug excreted in urine from formulation A &B

➢ **Absolute BA = $[(D_u)^{\infty}_{PO} / (D_u)^{\infty}_{IV}] x [dose_{IV} / dose_{PO}]$**

Where PO=perose & IV = intravenous

Conditions to be met for Urinary Excretion method to give valid results:

- Most useful for those drugs that are not extensively metabolized prior to urinary elimination.
- should be conducted only if at least 20% of a dose is excreted unchanged in the urine after IV dose
- Fraction of drug entering blood stream and excreted intact by the kidneys must remain constant
- Collection of urine has to continue until all the drug has been completely excreted (five times its half-life)



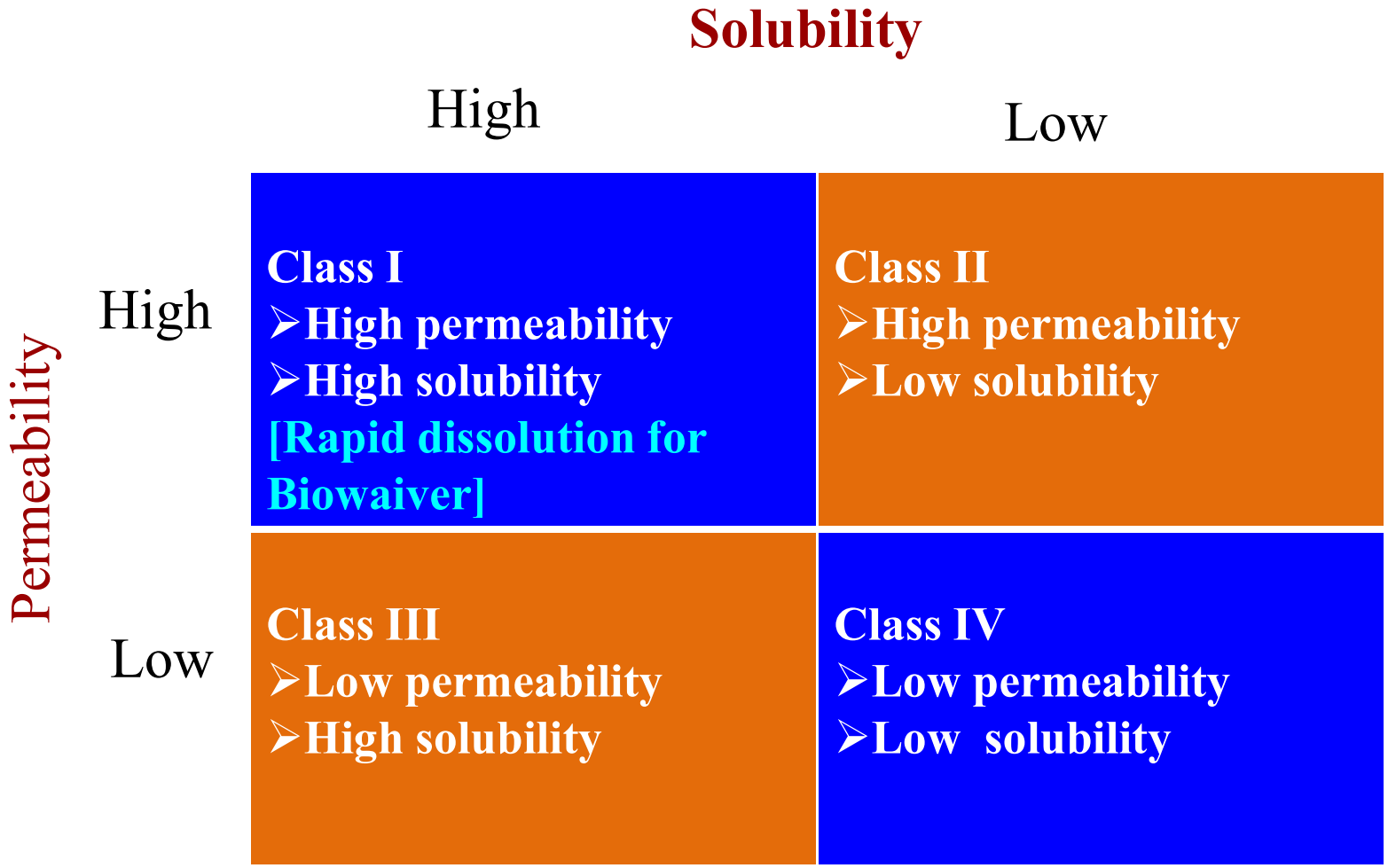
Typical variation in the concentration of drug in the sample of [A] plasma & [B]urine after administration of a single dose of a drug at time zero; in both cases the precise shape of the curve depends on type of drug under study

3.4.2. In Vitro approaches

- In vitro tests include weight variation, hardness , disintegration , dissolution, assay and content uniformity tests
- In vitro tests are usually used to assess product quality
- In **ideal circumstances** in vitro dissolution rate should correlate with in vivo bioavailability, i.e., a dosage form with a rapid dissolution rate is likely to have a rapid rate of drug bioavailability in vivo.

- However, BA of drug depends not only on **dissolution of drug product**, but also on such factors as :
  - Solubility of drug
  - Permeability of biological membrane to drug
  - Saturable presystemic metabolism
  - Drug instability in gastric fluid
  - Viscosity of dissolution medium[body fluid]
  - Drug complexation with such substances as:
    - concurrently administered drugs
    - food component
    - endogenous substances

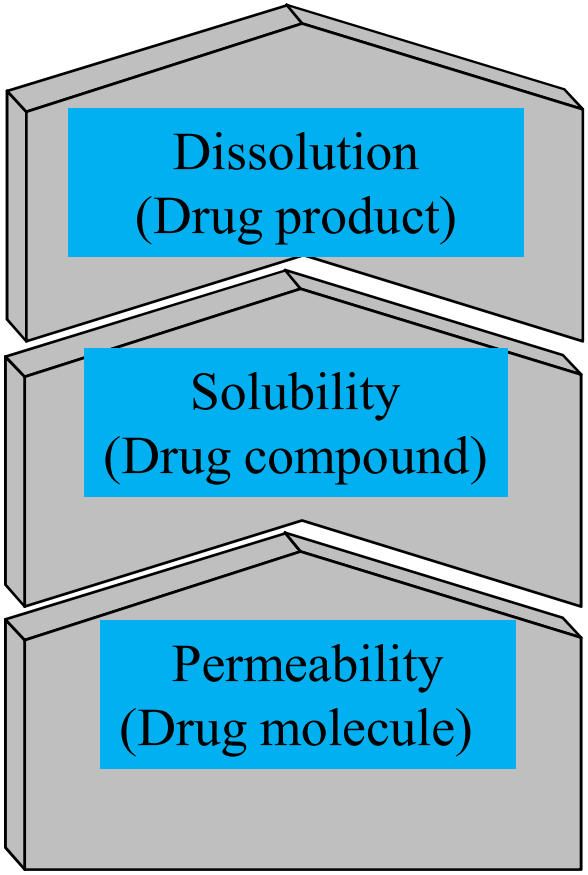
Biopharmaceutics Classification System [BCS]



Class boundaries

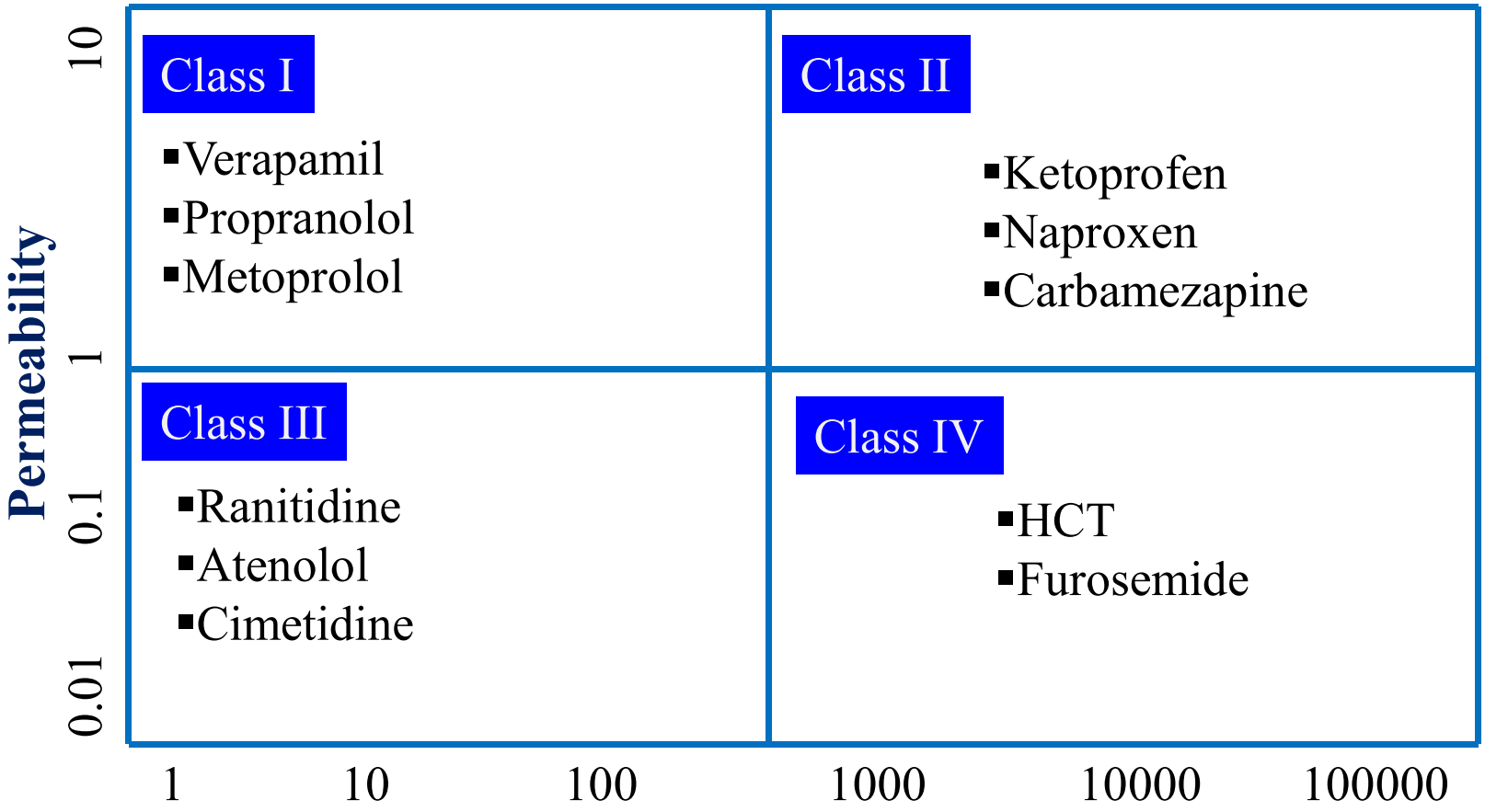
- **Highly soluble** :The highest dose strength is soluble in ≤ 250 ml water over a pH range of 1 to 7.5
- **Highly permeable:** When absorption extent in human is determined to be ≥ 90% of an administered dose
- **Rapidly dissolving:** When ≥ 85% of labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of ≤ 900 ml buffer solutions

BCS Class Boundaries: Objectives



- Rapid dissolution: Ensures that in vivo dissolution is not likely to be the "rate determining" step
- High solubility: Ensures that solubility is not likely to limit dissolution & hence, absorption of drug
- High permeability: Ensures that drug is completely absorbed during limited transit time through the small intestine

BSC system for selected model drugs



Volume required to dissolve the highest dose strength at the lowest solubility in pH 1-8 [Note: 1ml set as low value]

BCS implications for drug development

- Application in early drug development and then in the management of product change through its life cycle
- Aids fundamental understanding of biopharmaceutical & physical properties of the drug
- Aids discriminatory dissolution method development
- Can help guide development of in-vitro/in-vivo correlations
- Can be used to obtain a Biowaiver
- Development of poorly soluble drugs

IVIVC expectation for immediate release products based on BCS

Class	Solubility	Permeability	Absorption rate control	IVIVC expectations
I	High	High	Gastric emptying	IVIVC expected, if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlations
II	Low	High	Dissolution	IVIVC expected, if in vitro dissolution rate is similar to in vivo dissolution rate, unless dose is very high.
III	High	Low	Permeability	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution
IV	Low	Low	Case by case	Limited or no IVIVC is expected.

Applications of BCS in oral drug delivery technology

Class I - High Permeability& High Solubility

- Achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile.
- Formulation approaches include both control of release rate & certain physicochemical properties of drugs like pH-solubility profile of drug

Class II: High Permeability and Low Solubility

- Micronization
- Addition of surfactants
- Formulate as nano-emulsions & micro-emulsions systems
- Use complexing agents like Cyclodextrins

Class III - Low Permeability & High Solubility

- Require technologies that address to fundamental limitations of absolute or regional permeability.
  - Use absorption enhancer
- Peptides and proteins constitute part of class III and the technologies handling such materials are on rise now days

Class IV : Low Permeability and Low Solubility

- Major challenge for development of drug delivery system
- The route of choice for administering such drugs is parenteral by improving solubility using solubility enhancers
- Fortunately, extreme examples are the exception rather than the rule and are rarely developed and reach the market

Biowaiver

It is an exemption from conducting human bioequivalence studies

Conditions:

when the active ingredient(s) meet certain solubility and permeability criteria in vitro and when the dissolution profile of the dosage form meets the requirements for an "immediate" release dosage form

Biowaiver for

- Rapid and similar dissolution
- High solubility &High permeability
- Wide therapeutic window
- Excipients used in dosage form used previously in approved IR solid dosage forms

Limitations of BCS as a Predictor of Drug Disposition

- Permeability (90% absorption) is difficult to determine, and difficult to convince the regulatory agency
- There is little predictability for BCS classification drugs beyond Class I primarily due to difficulty of determining and proving 90% absorption.
  - Many drugs are misclassified (e.g. HIV protease inhibitors as Class 4 compounds)

In vitro-in vivo correlation [IVIVC]

- IVIVC is "predictive mathematical model describing relationship between in vitro property of the dosage form & in vivo response."
- The concept behind establishing IVIVC is that in vitro dissolution might serve as a surrogate for pharmacokinetic studies in humans
- Establishing IVIVC reduces number of bioequivalence studies performed during the initial approval process & when certain scale-up and post-approval changes in the formulation need to be made. Obtaining a satisfactory correlation is, of course, highly dependent on the quality of the input variables

Limitation of in vitro-in vivo correlation [IVIVC]

If there was in vitro -in vivo correlation, then in vitro test could serve as **indicator** of how product will perform in vivo. But not due to the following reasons & others:

- Well designed in-vitro dissolution test never reflect poor drug BA due to **presystemic metabolism**
- Dissolution studies would not predict poor BA due to **instability or insoluble complex formation in body fluid**
- No studies accurately correlated in- vitro & in-vivo data to the point that use of upper & lower limits for in-vitro dissolution parameters can be reliably used to predict in-vivo behaviour & thus, to replace in-vivo test.

Applications of dissolution testing

As a tool :

- in drug development
- in providing control of manufacturing process for batch release
- for identifying potential bioavailability problems
- to assess the need for further bioequivalence studies relative to scale-up and post-approval changes (SUPAC)
- to signal possible bioinequivalence of formulations

Note

- In-vitro methods are vital in dev't & optimization of dosage forms while in-vivo tests are essential in obtaining information on effects of medication in living organisms
- Ultimate evaluation on performance of a drug product under conditions expected in clinical therapy must be an in-vivo test
- Dissolution test is unlikely to entirely replace BA testing
- In vitro test never substituted for in vivo test

Bioequivalence

- A comparison of two or more products with respect to their bioavailability. i.e.,
- One brand or dosage form of a drug or supplement is equivalent to a reference brand or dosage form of the same drug or supplement in terms of various bioavailability parameters (FDA's regulation 21.CFR-320.1 1991).

- When a new formulation of an existing drug is developed, its bioavailability is generally evaluated relative to the standard formulation of the original [authenticate] drug
- Two products or formulations containing the same active ingredient are bioequivalent if their rates & extents of absorption are same

What do you mean by preparations of same drug are bioequivalent ?

- Two products of same drug are bioequivalent if,
  - ✓ They are **therapeutically equivalent**, and therefore interchangeable.
  - ✓ **Pharmaceutically equivalent** drug products where the rates/extents of bioavailability of the active ingredients are not significantly different under suitable test conditions.

- In general, the FDA considers two products to be "therapeutic equivalents" if they:
  - are bioequivalent (demonstrated by bioavailability measurement)
  - are in compliance with compendia standards for strength, quality, purity and identity
  - have been manufactured in compliance with GMP
  - are adequately labelled

Pharmaceutically equivalent drug products

- According to FDA, "pharmaceutical equivalents" are drug products that contain identical active ingredients and are identical in strength or concentration, dosage form, and route of administration.

Note:

- Pharmaceutical equivalents do not necessarily contain the same inactive ingredients
- The terms "pharmaceutical equivalents" and "chemical equivalents" are often used interchangeably
- In order for a drug product to be interchangeable with pioneer (innovator or brand) product, it must be both pharmaceutically equivalent & bioequivalent to innovator product

Summary

- Clinical study is useful in determining safety & efficacy of drug product
- Bioavailability studies are used to:
  - define effect of changes in physico-chemical properties of drug substance & effect of drug product (or dosage form) on PK of the drug
  - compare the bioavailability of the same drug (same salt or ester) from various drug products.
- If drug products are bioequivalent & therapeutically equivalent, then their clinical efficacy and safety profile are assumed to be similar and may be substituted for each other.
- For all extravasscular routes of administration, $0 \leq F \leq 1$

Illustration-1

Drug product	Dose (mg)	AUC (µg hr/ml)
Oral solution	200	89.1
Oral tablet	200	85.5
Iv bolus injection	50	37.5

1.Compute absolute bioavailability of drug from tablet
2.Compute absolute bioavailability of drug from solution
3.On the bases of above answers , compare ABA of drug from solution & tablet
4.Compute relative bioavailability of the drug
5.Comment on bioavailability of a drug from tablet & solution ?

1. $$ABA\ from\ tablet = \frac{AUCtab}{AUCiv} * \frac{dose\ iv}{dose\ oral}$$

$$= \frac{85.5}{37.5} * \frac{50}{200} = 0.57$$

Absolute bioavailability from tablet is 57 %

2. $$ABA\ from\ solution = \frac{AUCsol}{AUCiv} * \frac{dose\ iv}{dose\ oral}$$

$$= \frac{89.1}{37.5} * \frac{50}{200} = 0.594$$

Absolute bioavailability from solution is 59.4 %

3. Absolute bioavailability of the drug from solution dosage from is 1.042 times greater as compared to its bioavailability from tablet preparation.

4. Relative bioavailability [RBA]?

$$RBA\ from\ solution = \frac{AUCtab}{AUCsol} * \frac{dose\ sol}{dose\ tab}$$

$$= \frac{85.5}{89.1} * \frac{200}{200} = 0.9596$$

5. Percent RBA of drug from tablet is 95.96% as compared to same drug from oral solution.

Illustration-2

If two products ,A & B, each containing 100 mg of the same drug are orally administered & only 80 mg & 40 mg of drug is recovered from Product A & B unchanged in urine, respectively, answer the following questions:

1.What can be said about absorption of a drug from the two formulations ?

2.Find percent RBA of the drug from formulations

3.Find ABA of the drug

Note: Neither product resulted in excretion of the entire dose due to existence of other routes of elimination, e.g. metabolism).

2. When potassium penicillin G was administered intravenously to a group of volunteers only 80% of the 500 mg administered drug was recovered in urine unchanged. When same drug was administered orally, however only 280 mg of unaltered drug was recovered in urine.

Find:

1. ABA of potassium penicillin G.

2. RBA of same drug